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GUIDELINES

Saudi Clinical Practice Guidelines for Management of Axial Spondyloarthritis Disease

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ABSTRACT

Introduction: This guideline offers evidence-based recommendations for physicians and policymakers on managing axial spondyloarthritis (axSpA) in Saudi Arabia.

Methods: A panel of 14 experts in research methodology, rheumatology, family medicine, and clinical pharmacology in Saudi Arabia approved 45 questions related to the monitoring and treatment, pharmacological and non-pharmacological, of different subtypes of axSpA. We conducted a search of different databases, including PubMed, EMBASE, and the Cochrane Library, from 2010 to 2024 to identify systematic reviews, meta-analyses, and clinical studies related to the diagnosis and management of

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axSpA. To evaluate the certainty of the evidence and formulate recommendations, we employed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The expert panel voted electronically on each recommendation. A recommendation was finalized when over 70% of the voting panel agreed.

***Results*:** We issued 31 evidence-based recommendations and seven statements based on the experts' opinions, which are grouped into nine categories. This guideline recommends initiating non-steroidal anti-inflammatory drugs (NSAIDs) as the first-line therapy for patients with symptomatic axSpA. If NSAIDs are ineffective, second-line treatments such as tumor necrosis factor inhibitors (TNFis), interleukin-17 inhibitors (IL-17is), or Janus kinase inhibitors (JAKis) should be considered. Localized glucocorticoid injections are suggested as supplementary therapy for cases of isolated sacroiliitis, enthesitis, or peripheral monoarthritis not responding adequately to the treatment options.

***Conclusion*:** The Saudi clinical practice guidelines provide updated evidence-based recommendations for monitoring and treating adults with axSpA. These recommendations help guide the best practice for healthcare professionals in managing patients with axSpA in Saudi Arabia.

Keywords: Axial; Spondyloarthritis; Guidelines; Management

Key Summary Points

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease that primarily affects the axial skeleton. In Saudi Arabia, there is a lack of local guidelines for managing axSpA in various scenarios. Therefore, this guideline aims to provide evidence-based recommendations for physicians and policymakers on managing axSpA in Saudi Arabia.

For symptomatic axSpA, non-steroidal anti-inflammatory drugs (NSAIDs) at the highest tolerated dose are recommended as first-line therapy, along with patient education, physiotherapy, regular exercise, and smoking cessation. If sustained improvements are seen within 2 to 4 weeks, NSAIDs may be continued.

Second-line treatment options for active axSpA (Ankylosing Spondylitis Disease Activity Score based on C-reactive protein [ASDAS-CRP] ≥ 2.1) include tumor necrosis factor inhibitors (TNFis), interleukin-17 inhibitors (IL-17is), or Janus kinase inhibitors (JAKis). IL-17i is recommended for patients with severe psoriatic arthritis or enthesitis, while TNFi is suggested for those with inflammatory bowel disease (IBD) or uveitis.

For primary failure, switching to a biological disease-modifying antirheumatic drug (bDMARD) or a targeted synthetic DMARD (tsDMARD) with a different mechanism of action is recommended. For secondary failure, switching to a bDMARD or tsDMARD, whether with the same or a different mechanism, is suggested.

Monitor the disease every 3 to 6 months if remission or low activity is achieved, consider treatment tapering after 12 months, and re-evaluate the diagnosis if ASDAS-CRP remains ≥ 2.1.

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INTRODUCTION

Spondyloarthritis (SpA) is a broad term that includes various inflammatory musculoskeletal disorders. Axial spondyloarthritis (axSpA) primarily affects the spine and sacroiliac (SI) joints, while peripheral SpA includes peripheral manifestations such as dactylitis, enthesitis, and both symmetric and asymmetric arthritis [1–3].

AxSpA can be further classified on the basis of spine and/or SI joint structural changes [4]. The radiographic axSpA (r-axSpA) subtype, previously referred to as ankylosing spondylitis (AS), is characterized by definite structural damage to the SI joints visible on plain radiographs, as defined by the modified New York (mNY) criteria [5, 6]. In contrast, non-radiographic axSpA (nr-axSpA) does not show such changes on X-ray but may demonstrate active inflammation or structural lesions on magnetic resonance imaging (MRI) [5, 7]. Both subtypes are recognized under the broader classification criteria established by the Assessment of Spondyloarthritis International Society (ASAS) [8, 9].

According to ASAS criteria, the classification of axSpA relies on two approaches: the "imaging arm," which requires the presence of sacroiliitis on MRI along with one clinical feature. The second approach, or the "clinical arm," requires the presence of the human leukocyte antigen B27 (HLA-B27) and two clinical features. Imaging of the SI joint is essential for diagnosing axSpA [10]. While X-rays reveal late lesions, MRI can detect bone edema (inflammatory changes) and post-inflammatory alterations like erosions, ankylosis, sclerosis, and fatty changes. In nr-axSpA, inflammation is visible only on MRI. In contrast, in r-axSpA, structural changes can be seen on X-ray, computed tomography (CT), and MRI [11].

The most common symptom of axSpA among patients is low back pain, distinguished by inflammatory characteristics [12, 13]. Furthermore, axSpA may present with extra-musculoskeletal symptoms, including psoriasis, uveitis, and inflammatory bowel disease (IBD) [14].

The global prevalence of axSpA exhibits considerable variation among various published research, which is estimated to range from 0.3% to 1.4% worldwide [15–17]. In the Middle East, the prevalence of axSpA was assessed at 0.11% [18]. In Asia, axSpA was reported in 0.36% of the individuals, with a prevalence of 0.16% in East Asia and 0.06% in South Asia [18, 19]

The differences in the occurrence of SpA can be partially linked to geographic variations in the occurrence of the HLA-B27 antigen [10, 20]. HLA-B27 is linked with SpA, particularly axSpA, and is considered one of the factors that can predict radiographic progression [21, 22].

Consequently, axSpA substantially affects health-related quality of life (HRQoL) through functional limitations, diminished work productivity, and worse social connections [23]. The mental health of individuals with axSpA could be negatively impacted, with disease activity and employment status influencing the risk of developing depression and anxiety [24]. Moreover, extra-musculoskeletal manifestations of axSpA, such as uveitis and enthesitis, result in disease burden, poor outcomes, and increasing disease severity [23].

Timely diagnosis and appropriate treatment are essential for achieving optimal outcomes in patients with axSpA [25]. Appropriate treatment could enhance patients' HRQoL through symptom management, inflammatory control, structural damage prevention, functionality preservation, and promotion of social engagement. Moreover, maintaining the capacity to work is a primary goal in the management of axSpA [26].

Several international guidelines discussed the diagnosis and treatment of axSpA. In 2022, ASAS and the European League Against Rheumatism (EULAR) jointly updated evidence-based recommendations for managing axSpA [27]. In 2019, the American College of Rheumatology (ACR), Spondylitis Association of America, and SPARTAN provided updated guidance regarding using new medications in the United States of America (USA) for AS and nr-axSpA [28]. In 2023, the Pan American League of Associations for Rheumatology (PANLAR) developed their first recommendations for managing axSpA in the USA [29].

Consensus recommendations were published in 2024, which concluded the referral, monitoring, diagnosis, and management of axSpA in the Gulf region [30]. In Saudi Arabia, a guideline published in 2022 provides recommendations

for screening and referral of patients with axSpA based on expert points of view and available evidence. However, some situations were lacking, such as patients with axSpA and comorbidities, the role of surgery treatments, nutritional therapy, and specific drug classes used to treat patients with axSpA in Saudi Arabia [31].

Therefore, the existing guidelines were developed and enhanced by addressing gaps in the previous Saudi guidelines in managing and treating adult patients with axSpA in Saudi Arabia. This involves a comprehensive review of current practices and the integration of new and highest evidence to ensure that most aspects of axSpA management are effectively updated and covered.

SCOPE AND PURPOSE

These guidelines offer evidence-based recommendations for the clinical practice of treating adult patients with axSpA in Saudi Arabia. They focus on monitoring adults with axSpA, providing treatment and rehabilitation for adult axSpA, and other disease-related comorbidities, including uveitis, enthesitis, IBD, and during pregnancy.

Goal

To offer evidence-based recommendations that assist healthcare specialists in managing and treating Adult patients with axSpA in Saudi Arabia.

Objectives

The Saudi clinical practice guidelines provide practical guidance for the healthcare workers and stakeholders participating in managing patients with axSpA, aiming to:

1. Serve as a national reference for axSpA clinical practice that addresses the specific needs of local populations in Saudi Arabia.
2. Optimize the guide for different treatment modalities for managing different types of axSpA in Saudi Arabia.
3. Improve patient outcomes regarding symptom control, disease progression, and overall quality of life.
4. Guide identification and treatment strategies to minimize the impact of axSpA on patients' lives.

Guidelines Scope

1. What are evidence-based recommendations for monitoring axSpA among adult Saudi patients?
2. What are evidence-based recommendations on the pharmacological management of different types of axSpA among adult Saudi patients?
3. What are the evidence-based recommendations on the effects of non-pharmacological interventions for managing different types of axSpA among adult Saudi patients?
4. What are the evidence-based recommendations for comorbidities and special considerations associated with axSpA among adult Saudi patients?

End Users

These guidelines will benefit rheumatologists, general practitioners, physical therapists, and clinical pharmacists in Saudi Arabia. They offer valuable insights into axSpA management for healthcare decision-makers, researchers, and guideline developers. Additionally, end users may include patients who have been diagnosed with axSpA.

How Do We Use These Guidelines?

The Ministry of Health of Saudi Arabia aims to provide clinicians and their patients with guidelines for monitoring, managing, and treating axSpA among adults of all genders. Clinicians, patients, third-party payers, institutional review committees, and other stakeholders should not interpret these recommendations as absolute mandates. As discussed in

other guidelines that follow the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, no guideline or recommendation can encompass all the unique and often compelling aspects of individual clinical situations. Consequently, those responsible for assessing clinicians' actions should avoid applying these recommendations rigidly or uniformly.These guidelines were developed

Each recommendation is accompanied by statements that take into account values and preferences, resource use, feasibility, equity, acceptability, and other relevant factors. It is crucial to consider that these statements are essential for understanding the context of the recommendations. While the guideline provides valuable guidance, exercising sound clinical judgment in individual cases is essential. Clinicians should tailor their approach to each patient's unique needs and circumstances, considering the potential benefits and risks of different management strategies in their overall health and well-being.

METHODOLOGY

These guidelines were developed using the GRADE software [32].

Panel Composition

The Saudi axSpA guideline is a collaborative effort between the Ministry of Health, the Saudi Society of Rheumatology, and the Saudi Society of Clinical Pharmacy. A panel of 14 experts in research methodology, rheumatology, family medicine, and clinical pharmacology in Saudi Arabia contributed to its development, providing standardized, evidence-based recommendations for managing axSpA in Saudi Arabia. Furthermore, three of the rheumatologists were specialized in axSpA among the panel members.

Group Interaction and Process

The guidelines were created through a collaborative process employing the GRADE methodology, which facilitated open communication, consensus-building, and the incorporation of a range of expert viewpoints. This approach minimized potential biases and ensured that the recommendations were rooted in high-quality evidence. Panel members actively participated in discussions to define review protocols, evaluate the evidence's reliability, and develop well-supported recommendations. Each recommendation required ≥ 70% agreement among panelists to be approved. Disagreements during the evidence review and recommendation development process were resolved through discussion.

Selection of Questions and Outcomes' Prioritization

The guideline panel thoroughly examined recently published guidelines to identify key research questions [27, 29]. Subsequently, the panel discussed which Population, Intervention, Comparator, and Outcome (PICO) questions are essential for clinical practice in Saudi Arabia. In addition, the panel was allowed to suggest new PICO questions. After careful consideration, the panel developed 45 questions that were most relevant to clinical practice in Saudi Arabia (Table S1). The guideline panel reviewed and approved the final list of PICO questions. For each PICO, we used the GRADE approach to classify outcomes as critical, important, or unimportant [33]. Prioritized outcomes included treatment strategies, disease activity, progression, and occurrence of adverse events. The definitions of the prioritized outcomes are listed in Table 1.

Evidence Synthesis

The methodologists conducted an independent systematic literature review to inform the evidence to support the previously published guidelines. They comprehensively searched

Table 1 List of definitions

Term	Definition
ASAS 20 Improvement Criteria	To meet the ASAS 20 response criteria, improvements must be observed in four domains: patient global assessment, pain, function (measured by the BASFI, and inflammation (calculated as the mean of BASDAI questions 5 and 6). For a successful outcome, at least three domains must demonstrate a minimum improvement of 20% or greater, with each of these domains also showing an increase of at least one point on a 0–10 scale. Additionally, the remaining domains must not show any deterioration of 20% or more and must still demonstrate a minimum improvement of one point when measured on the same 0–10 scale [37]
ASAS 40 Improvement Criteria	It consists of four domains, akin to the ASAS 20 criteria. To achieve an ASAS 40 response, at least three domains must show a minimum improvement of at least 40% and an increase of two units on a scale from 0 to 10. In the rest of the domain, there should be no deterioration of 20% and a minimum elevation of one unit on the same scale [38]
ASAS 5/6 Improvement Criteria	It consists of six domains: patient global assessment, pain, function (assessed by BASFI), inflammation (mean of BASDAI questions 5 and 6), CRP, and spinal mobility (measured by lateral spinal flexion). To achieve the ASAS 5/6 improvement criteria, there must be a minimum of a 20% improvement in at least five domains [38]
ASAS-Health Index (HI)	It is a tool created by ASAS to evaluate the health of patients with SpA. It consists of 17 items with dichotomous answer options and evaluates various aspects of the patient's health, such as pain, emotional functions, sleep, sexual function, mobility, self-care, and community life [39, 40]
ASAS Partial Remission (ASAS-PR)	ASAS defines partial remission as a state reflecting very low disease activity. To qualify for ASAS partial remission, each of the following domains must have a value of 2 or less on a 0 to 10 scale [38]
Axial Spondyloarthritis Disease Activity Score (ASDAS)-Clinically Important Improvement (CII)	ASAS has established cutoffs for different disease activity states based on the ASDAS score. A change of ≥ 1.1 units in the ASDAS score is classified as a "clinically important improvement" [41]

Table 1 continued

Term	Definition
ASDAS Improvement Criteria	ASAS has established response criteria based on the ASDAS. A change of at least 1.1 units in the ASDAS score indicates a "clinically important improvement," while a difference of at least two units signifies a "major improvement" [41]
ASDAS Inactive Disease	A score below 1.3 is classified as "inactive disease" [41]
ASDAS-Low Disease Activity (LDA)	A score below 2.1 is classified as "low disease activity" [41]
ASDAS-Major Improvement (MI)	A change of ≥ 2.0 units in the ASDAS score is classified as a "major improvement" [41]
Ankylosing Spondylitis spine MRI activity (ASspiMRI-a)	ASspiMRI-a assesses the activity of MRI lesions in the spine. It scores acute changes depending on the extent of bone marrow edema in each VU. A VU is the space between two imaginary lines drawn parallel to the end-plates of each vertebra. Scores 1:3 indicate acute changes with bone marrow edema, while scores 4 and 6 indicate spinal lesions with edema and erosions. Erosions without bone marrow edema are considered inactive. The score involved all 23 VUs from C2 to S1 (a total of 138) [42]
BASDAI 50 Response	The response to TNFi is defined by at least a 50% improvement in the BASDAI score or an absolute difference of two units after 3 months of therapy, along with an expert opinion indicating improvement [43]
Biosimilars	Biologic products have comparable clinical efficacy and safety to the FDA-approved biological products and lower costs. Common biosimilars are infliximab, adalimumab, And etanercept [44]
Disease-modifying antirheumatic drugs (DMARDs)	They are used in case of non-sufficient response to NSAIDs in SpA. Recently, DMARDs have been categorized into two groups: synthetic DMARDs and biological DMARDs. Synthetic DMARDs include conventional agents (csDMARDs) such as methotrexate, sulfasalazine, and leflunomide, as well as targeted synthetic DMARDs (tsDMARDs), which are small molecules that target intracellular pathways. Approved biological DMARDs (bDMARDs) for SpA include various TNFi for AS and nr-axSpA, along with IL-17A such as secukinumab for AS with radiographic involvement [45]

Table 1 continued

Term	Definition
Harris Hip Score (HHS)	A clinician-performed and clinical-based outcome scale to assess hip joint disease activity and function. It consists of 10 items focusing on four primary categories, including pain, function, range of motion, and deformity, with a maximum total score of 100 [46]
Low disease activity	Low disease activity is best defined by reaching an ASDAS score of 1.3–2.1 [41]
Low dose	Lesser than the recommended dose for treating SpA
Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)	MASES is a clinical scoring system to evaluate enthesitis in patients with AS, SpA, and PsA in 13 anatomical sites for enthesitis. Each site is scored for tenderness with a value of 0 or 1, leading to a total score ranging from 0 to 13 [47, 48]
Modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)	It is an adjustment of the SASSS, and it only assesses the lumbar and cervical spines from the lateral view. The total mSASSS score is calculated by summing the scores of 24 vertebral edges, with a possible range from 0 to 72. Absolute change in the score corresponds to the structural damage progression among patients with AS [49]
Primary failure	No response or insufficient therapeutic efficacy within 6 months of treatment initiation [50]
Remission	Remission is reached when (1) the sum score in these four domains: pain represented by the VAS score (0–100); function represented by the BASFI score (0–100); inflammation represented either by the mean of the two mornings stiffness-related BASDAI questions (item 5 or 6) is < 20 on a 0–100 scale [37], or (2) ASDAS score < 1.3 or 3 [51, 52]
Secondary failure	Response achieved within 6 months, followed by subsequent loss, or a decline in efficacy over time [50]
Severe pain	Pain that extends beyond the typical tissue healing period of 3 months is characterized by intense back pain that significantly impairs daily activities and does not respond to standard treatments for axSpA without being linked to an inflammatory process

Table 1 continued

Term	Definition
Spondyloarthritis Research Consortium of Canada (SPARCC) score	The SPARCC scoring system evaluates edema-like signal alterations in the spine and SI joint MRI among patients with spondyloarthritis. Each SI joint is divided into four quadrants by a line that bisects the joint and its perpendicular line and is scored for the presence or absence of BME to 0 or 1, for a maximum score of 8. Additional points for each continuous edema-like signal of depth ≥ 1 cm from the articular surface and very high signal intensity, for a maximum additional four scores, and the maximum SPARCC score is 72, with higher values indicating disease progression [53]
Usual care	It is the treatment approach following the standard of care recommended by the patient's rheumatologist

AS ankylosing spondylitis, *ASAS* Assessment of Spondyloarthritis International Society, *ASAS-HI* ASAS-Health Index, *ASAS-PR* ASAS-Partial Remission, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *ASDAS-CRP* ASDAS based on C-reactive protein, *ASDAS-CII* ASDAS-Clinically Important Improvement, *ASDAS-LDA* ASDAS-Low Disease Activity, *ASDAS-MI* ASDAS-Major Improvement, *axSpA* axial spondyloarthritis, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BME* bone marrow edema, *CRP* C-reactive protein, cs-*DMARDs* conventional synthetic disease-modifying antirheumatic drugs, *DMARDs* disease-modifying antirheumatic drugs, *FDA* Food and Drug Administration, *HHS* Harris Hip Score, *IL-17A* Interleukin-17A, *MASES* Maastricht Ankylosing Spondylitis Enthesitis Score, *mSASSS* Modified Stoke Ankylosing Spondylitis Spine Score, *MRI* magnetic resonance imaging, *NSAIDs* non-steroidal anti-inflammatory drugs, *PsA* psoriatic arthritis, *SASSS* Stoke Ankylosing Spondylitis Spine Score, *SI* sacroiliac, *SPARCC* Spondyloarthritis Research Consortium of Canada, *TNFi* tumor necrosis factor inhibitors, *tsDMARDs* targeted synthetic disease-modifying antirheumatic drugs, *VAS* visual analog scale, *VU* vertebral unit, *ASspiMRI-a* Ankylosing Spondylitis Spine MRI Activity

medical databases (PubMed, EMBASE, and the Cochrane Library) using specific search terms tailored to each research question. Two experts in research methodology and a medical literature specialist assisted in this process. The search terms used for each question are available (Supplementary Material). All relevant systematic reviews and individual randomized controlled trials (RCTs), non-randomized trials, post hoc analyses, and pooled analyses published between 2010 and 2024 were extracted from the databases. If insufficient evidence was found for a particular question, we expanded our search to include studies published before 2010.

Title and abstract screening were conducted by two independent authors on the retrieved citations, and studies that met the inclusion criteria for each PICO question were included. The same reviewers assessed the full texts of potentially eligible studies for final inclusion.

We prioritized the inclusion of recent studies in our guidelines. To assess the quality of these RCTs, two independent reviewers used the established criteria of the Cochrane risk of bias tool to assess the risk of bias [34]. The assessment was performed using the Newcastle–Ottawa scale for non-RCTs [35].

When more than one eligible study was available for a given question, we prioritized the most recent and comprehensive studies, particularly those with larger sample sizes and longer follow-up durations. Preference was also given to studies with a lower risk of bias and those that provided direct evidence applicable to the population and clinical setting in Saudi Arabia.

For each outcome, we used the GRADE approach to determine the certainty of the

evidence. The certainty of the evidence was classified as "high," "moderate," "low," or "very low" depending on the following domains: study design, risk of bias, publication bias, consistency in the findings, indirectness of evidence, and imprecision of the estimate [36].

Assessing the Certainty of Evidence

We used the GRADEpro guideline development tool [32] for each PICO question to generate evidence profiles containing critical and important outcome absolute and relative effects and certainty assessment.

After assessing the five domains of GRADE, the certainty was categorized as very low, low, moderate, and high [33]. High certainty indicates strong confidence that the actual effect is close to the estimated effect. Moderate certainty suggests a moderate degree of confidence, meaning the true effect will likely be near the estimate. Low certainty suggests limitations in the effect estimate, and the true effect may vary significantly. Very low certainty reflects a high level of uncertainty regarding the effect estimate, highlighting the need for further research to clarify this uncertainty.

Formulation of Recommendations

Each recommendation was formulated considering the risk–benefit ratio, the quality of the available evidence for each intervention, and the panel's clinical experience. After stating the recommendations, they were revised through virtual meetings. The revised recommendations were presented to the expert panel for voting on the GRADEpro system, and at least 70% of the consensus was required to pass.

The recommendations could be either in favor or against the intervention. In addition, the strength of the recommendation is categorized as strong or conditional. Conditional recommendations are issued on the basis of low or very low certainty evidence when supported by additional contextual factors, such as expert consensus, values and preferences, or when the overall benefits outweigh the potential risks. Understanding the implications of the recommendation's strength is crucial for informed decision-making (Table 2).

Ethical Considerations

This article is based on previously conductedstudies and does not contain any new studieswith human participants or animals performedby any of the authors. All panelists who contributed to the consensus process are listed as authors on this paper. All studies were previously published, and no informed consent wasnecessary or obtained for inclusion in these guidelines.

RECOMMENDATIONS

1. It is critical to diagnose axSpA using the ASAS criteria accurately. This is a cornerstone for implementing targeted therapeutic interventions and achieving optimal patient outcomes. Using these standardized criteria allows healthcare providers to distinguish axSpA from other rheumatological conditions and aids in early disease recognition, essential for preventing irreversible structural damage and preserving patients' quality of life [10]. The ASAS criteria include two parallel yet complementary diagnostic approaches: the imaging arm and the clinical arm. The imaging arm mandates the presence of sacroiliitis, along with at least one feature of SpA. For the clinical diagnosis, HLA-B27 is required, along with at least two additional features of SpA. This dual-pathway approach ensures comprehensive patient evaluation while maintaining diagnostic accuracy. This step lays the foundation for effective management and treatment outcomes [54].
2. AxSpA demands a comprehensive, multidisciplinary management approach that integrates various healthcare specialists to address its complex manifestations and optimize patient outcomes. This collaboration is fundamental to delivering care that addresses both the primary musculoskeletal symptoms and the diverse extra-articular manifestations of the disease [4]. Rheumatologists are the

Table 2 Implications of the recommendation's strength

Strength of recommendation	Definition	Implications for stakeholders
Strong recommendation	The advantages of the intervention exceed the hazards, and the quality of evidence is high	Clinicians should follow this recommendation in most situations. Patients can be confident in the benefits of the intervention
Conditional recommendation	The advantages of the intervention exceed the hazards, but the quality of evidence is lower, or there is uncertainty	Clinicians should consider this recommendation, but individual patient circumstances and preferences should guide decision-making. Patients should be informed about the uncertainty and involved in the decision process
No recommendation	There is no sufficient evidence to either back up or oppose the intervention	Clinicians should use their judgment and consider patient preferences. More research is warranted to clarify the efficacy of the intervention
Weak recommendation against	The hazards of the intervention exceed the advantages, but the evidence quality is low	Clinicians should generally avoid this intervention, but individual cases may warrant its use. Patients should be made aware of the probable hazards
Strong recommendation against	The risks of the intervention clearly outweigh the benefits, and the quality of evidence is high	Clinicians should not use this intervention. Patients should be made aware of the strong evidence against its use

key professionals accountable for coordinating care, as they provide diagnostic expertise, treatment planning, and ongoing disease monitoring. Their specialized knowledge in inflammatory arthritis enables them to initiate and adjust appropriate pharmacological interventions, including csDMARDs and biological therapies when indicated. Additionally, physical therapists would provide strategies for managing daily activities and maintaining workplace productivity while protecting joint health. The multisystem nature of axSpA necessitates coordinated specialist care to address its various extra-articular manifestations. Ophthalmologists are crucial in monitoring and treating acute anterior uveitis, which affects almost one-third of patients with axSpA, requiring careful oversight to maintain vision. For gastrointestinal complications, gastroenterologists manage the concurrent IBD present in 5–10% of cases, ensuring treatments benefit both conditions. Similarly, dermatologists provide essential expertise in managing psoriasis and other cutaneous manifestations that occur in approximately 10% of patients, carefully balancing skin and joint treatments for optimal outcomes. This integrated specialist care approach helps ensure comprehensive disease management and improved patient outcomes [55, 56].

3. A target-oriented treatment strategy for axSpA centers on systematically monitoring disease activity under rheumatologist supervision using validated composite scores every 3–6 months. For patients with steadily active disease in spite of conventional treatment, discussing treatment escalation with biological drugs is important, taking into account the patient's clinical profile and access to therapy. This approach aims to achieve either remission or low disease activity state, thereby reducing the impact on function and quality of life. Regular assessment using validated measures enables healthcare providers to evaluate treatment responses objectively and make timely therapeutic adjustments through shared decision-making between patients and rheumatologists. This systematic monitoring helps identify the need for treatment modification early, potentially improving long-term outcomes while ensuring standardized documentation of disease activity parameters [57].
4. Non-pharmacologic strategies play a vital role in managing axSpA. These interventions include physical therapy, which provides specific interventions that focus on spinal mobility, posture correction, and muscle strengthening. Professional physical therapists can develop individualized programs that address specific limitations and help patients maintain optimal joint function while preventing further mobility restrictions. Another strategy is to enhance patient education by providing comprehensive knowledge about their condition, including disease progression, lifestyle modifications, and self-management strategies. Understanding the disease flares and treatment options has a positive effect on the patients. Regular exercise is another effective intervention, particularly a combination of aerobic activities and flexibility training, that helps maintain spinal mobility, improves cardiovascular health, and reduces disease-related fatigue and stiffness. Finally, smoking cessation is crucial as tobacco use is associated with increased disease activity, more severe radiographic progression, and reduced treatment efficacy in patients with axSpA. These methods are effective in improving mobility, reducing discomfort, and enhancing overall well-being [27, 58].
5. Patients' engagement in shared decision-making about their treatment is crucial for achieving optimal health outcomes. By thoroughly explaining the available treatment options and taking patient preferences into account, healthcare providers can enhance treatment adherence and boost overall patient satisfaction [59]. Implementing shared decision-making requires improving physicians' communication skills and educating patients about participation. Challenges for doctors include time constraints and the need for specific skills to establish partnerships with patients. However, involving patients in decision-making may not significantly increase consultation length. Self-

management programs have been shown to reduce unplanned hospitalizations for various chronic conditions. Various approaches to support patient engagement include information leaflets, online peer support, counseling, and educational sessions [60].

These key recommendations for managing axSpA are summarized in Table 3. The final guideline statements and recommendations are presented in Table 4.

1. Diagnosis and Assessment of Adults with Active Axial Spondyloarthritis (axSpA)

Recommendation 1: *We suggest using treat-to-target (T2T) management to measure disease activity in adults with an axSpA instead of using the usual care "a standard of care approach according to the treating rheumatologist of the patient" (conditional recommendation, low certainty of evidence).*

Rationale

This recommendation was informed by a cluster-randomized, controlled, open-label trial (TICOSPA trial) ($N = 160$) comparing the advantages of a tight control/treat-to-target strategy (TC/T2T) versus usual care in patients with axSpA [61]. The proportion of patients achieving improvements of ≥ 20% (assessed by ASAS 20), ≥ 40% (assessed by ASAS 40), and ≥ 50% (assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI 50)) were non significantly greater in the T2T group in comparison with the usual care group (risk ratio [RR] 1.04, 95% confidence interval [CI] 0.81–1.34; low certainty; RR 1.35, 95% [CI] 0.83–2.21; low certainty; and RR 1.49, 95% CI 0.99–2.24; low certainty; respectively, Table S2). Additionally, there was no significant difference in the percentage of patients achieving Ankylosing Spondylitis Disease Activity Score – Low Disease Activity (ASDAS-LDA), ASDAS-Clinically Important

Table 3 Summary of the principles of management of axial spondyloarthritis (axSpA)

Principles of management of axial spondyloarthritis (axSpA)	Panel agreement %
1. It is critical to accurately diagnose axSpA using the ASAS criteria. This step lays the foundation for effective management and treatment outcomes [10]	100
2. AxSpA is a multifaceted condition that needs a collaborative approach including various healthcare professionals, including rheumatologists, physical therapists, and other specialists (ophthalmologists, gastroenterologists, dermatologists). This teamwork is essential to address the wide range of symptoms associated with the disease, such as those affecting the eyes, skin, and digestive system [4]	100
3. For individuals with active axSpA, adopting a target-oriented treatment strategy according to ASDAS-CRP criteria is advisable. Consistent monitoring of disease activity enables healthcare providers to modify treatment plans dynamically, aiming for minimal disease activity or complete remission [57]	100
4. Non-pharmacologic strategies, including physical therapy, patient education, regular exercise, and smoking cessation, play a vital role in managing axSpA. These methods are effective in improving mobility, reducing discomfort, and enhancing overall well-being [27]	100
5. Engaging patients in shared decision-making about their treatment is crucial for achieving optimal health outcomes. By thoroughly explaining the available treatment options and taking patient preferences into account, healthcare providers can enhance treatment adherence and boost overall patient satisfaction [59]	100

ASAS Assessment of Spondyloarthritis International Society, *ASDAS-CRP* Ankylosing Spondylitis Disease Activity Score based on C-reactive protein, *axSpA* axial spondyloarthritis

Table 4 Strength and level of evidence for the recommendations for adults with active axial spondyloarthritis (axSpA)

Recommendations	Strength of recommendation	Certainty of evidence	Percentage of panel agreement %
1. Diagnosis and assessment of adults with axSpA			
1. We *suggest* using T2T management to measure disease activity in adults with an axSpA instead of using the usual care	Conditional	Low	92
2. We *suggest* using ASDAS-CRP to assess disease activity in adults with an axSpA over standard care	Conditional	Very low	10
3. We *recommend* frequent monitoring every 3–6 months for adults with an axSpA, particularly when starting a new therapy, rather than less frequent monitoring every 12 months or more. The specific frequency should be tailored based on individual symptoms, severity, and treatment needs	Strong	Moderate	100
2. First-line treatments for adults with axSpA			
4. We *recommend* starting therapy with NSAIDs for symptomatic patients, using them as the primary treatment for 2 to 4 weeks. Thereafter, we *suggest* on-demand use based on symptoms Remarks: For symptomatic adult patients with an active axSpA, we *suggest against* continuous NSAIDs treatment. Continuous treatment may be associated with the risk of gastrointestinal bleeding, kidney injury, and cardiovascular disease	Strong	Moderate	85
5. For adults with active axSpA requiring non-steroidal anti-inflammatory treatment, we *suggest* using either standard NSAIDs or COX-2 inhibitors. Remarks: COX-2 inhibitors may be preferred for patients with a history of gastrointestinal complications or IBD, as they are associated with a lower risk of gastrointestinal side effects compared to regular NSAIDs	Conditional	Very low	100

Table 4 continued

Recommendations	Strength of recommendation	Certainty of evidence	Percentage of panel agreement %
3. Second-line treatments for adults with axSpA			
6. For adults with active axSpA despite NSAIDs treatment, we *recommend* using either TNFi (including infliximab, etanercept, certolizumab, adalimumab, and golimumab), IL-17i (ixekizumab, secukinumab, and bimekizumab), or JAKi (upadacitinib and tofacitinib)	Strong	Moderate	100
7. For adults with active axSpA, we *suggest* using any TNFis	Conditional	Low	100
8. For adults with active axSpA, we *suggest* using TNFi as monotherapy rather than in combination with NSAIDs Remarks: Chronic NSAIDs use alongside TNFi does not significantly enhance effectiveness compared to TNFi alone. Additionally, long-term NSAIDs use is associated with serious risks, including gastrointestinal bleeding and renal impairment. The panel advises using NSAIDs on an as-needed basis to control pain unrelated to inflammation, such as pain from degenerative causes	Conditional	Low	92
9. For patients with active nr-axSpA, we *recommend* using TNFi, (infliximab, etanercept, certozilumab, adalimumab, and golimimab), IL-17i (ixekizumab secukinumab, and bimekizumab), or JAKi (upadacitinib)	Strong	Moderate	92
4. Management of adults with axSpA and comorbidities			
10. For adults with active axSpA and IBD, we *suggest* using either monoclonal TNFi or JAKi (upadacitinib or tofacitinib)	Conditional	Very low	100
11. For adults with axSpA and active IBD, we *recommend against* using IL-17i medications over no treatment	Strong	High	100

Table 4 continued

Recommendations	Strength of recommendation	Certainty of evidence	Percentage of panel agreement %
12. For adults with axSpA and IBD, we *suggest* using COX-2i over NSAIDs if needed, specifically after the gastroenterology consultation Remarks: COX-2i are safer than traditional NSAIDs for patients with IBD, particularly regarding gastrointestinal complications	Conditional	Low	100
13. For adults with axSpA and acute episodes of uveitis, we *recommend* using TNFi monoclonal antibodies (preferably adalimumab and or infliximab) over etanercept	Strong	Moderate	92
14. For adults with axSpA and uveitis, we *suggest* against using JAKi	Conditional	Moderate	92
5. Management of adults with axSpA and specific manifestation			
15. For adults with axSpA and enthesitis, we *suggest* using either IL-17is (such as secukinumab, ixekizumab, and bimekizumab), TNFi (infliximab, etanercept, certozilumab, adalimumab, and golimimab), or JAKi (upadacitinib and tofacitinib)	Conditional	Moderate	100
16. For adults with axSpA and enthesitis, the use of locally administered corticosteroids can be considered	Good practice statement		100
17. For pregnant women with active axSpA, we *suggest* using NSAIDs with caution if there is persistent pain despite approved therapy like TNFi Remarks: NSAIDs should be used cautiously during pregnancy, and NSAIDs should be avoided during the third trimester due to potential risks such as premature ductus arteriosus closure and reduced amniotic fluid	Conditional	Moderate	100
18. For pregnant women with axSpA and isolated sacroiliitis, we *suggest* using US-guided SI joint injections after the failure of TNFi therapy over no treatment	Conditional	Very low	92

Table 4 continued

Recommendations	Strength of recommendation	Certainty of evidence	Percentage of panel agreement %
19. For adults with axSpA and active peripheral joint involvement, we *advise* the use of intra-articular injections of glucocorticoids after the failure of conventional therapy (sulfasalazine) over no treatment, while we advise against using systemic glucocorticoids	Good practice statement		85
6. Long-term management of adults with axSpA			
20. For adults with active axSpA who have experienced primary failure on a TNFi, we *suggest* switching to non-TNFi medications (IL-17i or JAKi) rather than cycling to another TNFi and switching to another bDMARD or tsDMARD, with either the same or a different mechanism of action among patients experiencing secondary failure	Conditional	Very low	100
21. For adults with axSpA in remission, we *suggest* tapering treatment after 12 months of sustained remission over no tapering	Conditional	Low	92
22. For adults with axSpA who have maintained persistent remission for more than 12 months, we *suggest* either tapering or spaced-interval TNFi	Conditional	Very low	100
23. For adults with axSpA who have maintained persistent remission for more than 12 months, we *suggest* tapering TNFi therapy rather than discontinuing it Remarks: Tapering treatment helps reduce healthcare costs, minimize side effects, and address patient preferences	Conditional	Low	100
24. For adults with axSpA in remission for more than 12 months, we *suggest* tapering JAKi rather than stopping them abruptly	Conditional	Low	100

Table 4 continued

Recommendations	Strength of recommendation	Certainty of evidence	Percentage of panel agreement %
25. For adults with axSpA in sustained remission or low disease activity for at least 12 months, we *suggest* using either low-dose IL-17is or spaced intervals of IL-17is. However, we advise against the abrupt discontinuation of IL-17 inhibitors	Conditional	Low/moderate	85
26. For adults with axSpA with active sacroiliitis despite second-line therapy, we *suggest* using SI injection of glucocorticoids over no treatment	Conditional	Very low	92
27. For patients with moderate to severe pain following the failure of previously recommended treatments, we *advise against* the routine use of opioids	Good practice statement		92
7. Monitoring of adults with active axSpA			
28. For adults above 50 years with axSpA, we *suggest* evaluation and regular screening for osteoporosis using bone mineral density and fracture risk over no screening Remarks: Assessment and management of osteoporosis is essential, particularly in patients with a long disease duration, or high-risk groups such as those on corticosteroids or patients above 50 years who are prone to higher risk of fracture	Conditional	Very low	100
29. For monitoring disease progression in adults with axSpA, we *suggest* regular radiological assessments, such as an SI joint X-ray every 2 years, rather than no monitoring. We do not recommend routine follow-up MRIs of the SI joint or spine unless there is uncertainty regarding the source of persistent symptoms or inflammatory activity. In such cases, MRI may help determine the presence of inflammation and guide therapeutic decisions	Conditional	Low	85
8. Non-pharmacological management of patients with axSpA			
30. For adults with axSpA, we *suggest* using an anti-inflammatory diet, such as a Mediterranean diet, over a regular diet	Conditional	Very low	92

Table 4 continued

Recommendations	Strength of recommendation	Certainty of evidence	Percentage of panel agreement %
31. For adults with axSpA, we *suggest* using alternative treatments such as omega-3 and fish oil over no treatment	Conditional	Very low	85
32. For adults with axSpA, we *suggest* using regular physical therapy and exercise over not using it	Conditional	Low	100
33. For adults with axSpA, we *suggest* using active physical therapy (supervised exercise) over home exercise	Conditional	Low	92
34. For adults with axSpA, we *suggest* active physical therapy over passive physical therapy	Conditional	Low	100
35. For adults with axSpA, smoking cessation is *strongly advised* to improve general health and enhance the quality of life	Good practice statement		
36. For patients with axSpA, it is essential to provide comprehensive education about the disease to all individuals	Good practice statement		
9. Surgical management of patients with axSpA			
37. For adults with axSpA experiencing disability or refractory pain due to hip joint structural damage, we *advise* considering total hip arthroplasty	Good practice statement		85
Remarks: Total hip arthroplasty has a great impact on a patient's mobility and quality of life, but the yield of the surgical intervention depends objectively on individual clinical, surgical risk profile, type of prosthesis/fixation method, and surgical approach			
38. For adults with axSpA and thoracolumbar kyphotic deformity, the decision to proceed with lumbar osteotomy should be guided by the severity of the deformity, the patient's functional status, and a careful evaluation of surgical risks versus benefits	Good practice statement		100

ASDAS-CRP Ankylosing Spondylitis Disease Activity Score based on C-reactive protein, *axSpA* axial spondyloarthritis, *JAKi* Janus kinase inhibitors, *TNFi* tumor necrosis factor inhibitors, *IL-17* interleukin-17, *IL-17i* interleukin-17 inhibitors, *IBD* inflammatory bowel disease, *NSAIDs* non-steroidal anti-inflammatory drugs, *COX-2* cyclooxygenase-2, *COX-2i* cyclooxygenase-2 inhibitors, *SI* sacroiliac, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *T2T* treat-to-target, *MRI* magnetic resonance imaging, *nr-axSpA* non-radiographic axial spondyloarthritis, *THA* total hip arthroplasty, *US* ultrasound

Improvement (ASDAS-CII), and ASDAS-Major Improvement (ASDAS-MI) between the two groups (RR 1.12, 95% CI 0.79–1.60; low certainty; RR 1.33, 95% CI 0.86–2.06; low certainty; and RR 1.74, 95% CI 0.73–4.15; low certainty, respectively, Table S2). Regarding adverse events, the T2T group showed a non-significantly higher incidence in comparison with the usual care group (RR 1.35, 95% CI 0.85–2.16; low certainty, Table S2). Although this trial did not reveal a superiority of the T2T strategy compared to usual care, a greater percentage of patients in the T2T group achieved a ≥ 30% improvement on the ASAS-HI (47.3%) in comparison with the usual care group (36.1%) after 1 year. However, this difference was not statistically significant.

Therefore, the guideline panel deemed the intervention probably feasible, acceptable, and a large saving from a societal health economic perspective. In addition, they judged undesirable effects to be moderate. Other international guidelines align with our recommendation [27, 29].

Recommendation 2: *We suggest using an ASDAS-C-reactive protein (ASDAS-CRP) to assess disease activity in adults with axSpA over standard care (a standard of care approach according to the treating rheumatologist of the patient) (conditional recommendation, very low certainty of evidence).*

Rationale

This recommendation was based on a prospective observational study comparing the ASDAS versus the conventional clinical measures of disease activity in patients with axSpA treated with tumor necrosis factorinhibitors (TNFis) ($N = 60$) [62]. The study indicated that after 22 weeks, the change was significantly higher using the change in ASDAS-CRP versus change in CRP as individualized marker (mean difference [MD] 0.79; very low certainty, Table S3), change in MRI SI joint inflammation (MD 0.46; very low certainty, Table S3), change in total inflammation (MD 0.34; very low certainty, Table S3), and change in the BASDAI (MD 0.76; very low certainty, Table S3) [62]. The study concluded that ASDAS is a valid and responsive measure of disease activity in patients with axSpA treated with TNFi, outperforming traditional measures like CRP and BASDAI [62].

The ASDAS has validated cutoff values for assessing disease activity, recognized by both the Outcome Measures in Rheumatology (OMERACT) and the ASAS [41, 63]. In 2016, the ASAS-EULAR recommendations for axSpA recognized ASDAS as the preferred method for evaluating disease activity, particularly in patients with high disease activity and those receiving bDMARDs [27]. Moreover, it was indicated that the established cutoffs for ASDAS-CRP are more aligned with clinical outcomes compared with ASDAS-ESR [64].

The guideline panel deemed the intervention to be probably acceptable and feasible. On the other hand, this recommendation is conditional and based on very low certainty of evidence, indicating the need for further research to strengthen these findings.

Recommendation 3: *We recommend frequent monitoring every 3–6 months for adults with an axSpA, particularly when starting a new therapy, rather than less frequent monitoring every 12 months or more. The specific frequency should be tailored based on individual symptoms, severity, and treatment needs (strong recommendation, moderate certainty of evidence).*

Rationale

Indirect evidence was used to address this recommendation because of the lack of direct evidence. A meta-analysis of 55 RCTs and cohort studies ($N = 3976$) evaluated the impact of TNFi on the spine and SI joint inflammation in patients with axSpA, as assessed by MRI at various follow-up intervals [65]. The disease activity after 12 weeks, as assessed by the SPARCC score in the spine and the SI joint, showed a reduction in the TNFi group in comparison with the placebo (MD − 4.85, 95% CI − 10.99 to 1.28 and MD − 3.19, 95% CI − 4.8 to − 1.58; moderate certainty; respectively, Table S4). When disease activity was evaluated by the ASspiMRI-a, the TNFi group demonstrated a greater reduction after 13 weeks compared to the control (MD − 1.67, 95% CI − 5.2 to 1.87; low certainty, Table S4). However, after 2 years of follow-up,

the results favored the control (MD 1.34, 95% CI − 6.3 to 8.98; low certainty, Table S4).

The guideline panel determined that frequent monitoring is acceptable, likely cost-effective, feasible, and may enhance equity. Therefore, they strongly recommended frequent monitoring every 3 to 6 months. However, the exact frequency should be decided individually, depending on symptoms, severity, and treatment, which aligns with other international guidelines [29].

2. First-Line Treatment for Adults with Active Axial Spondyloarthritis (axSpA)

Recommendation 4: *We recommend starting therapy with Nonsteroidal anti-Inflammatory drugs (NSAIDs) for symptomatic patients, using them as the primary treatment for 2 to 4 weeks (strong recommendation, moderate certainty evidence). Thereafter, we suggest on-demand use based on symptoms.*

Remarks: For symptomatic adult patients with active axSpA, we suggest against continuous NSAIDs treatment. Continuous treatment may be associated with the risk of gastrointestinal bleeding, kidney injury, and cardiovascular disease.

Rationale

Our recommendation is based on an RCT study ($N = 167$) that aimed to compare the effect of continuous versus on-demand therapy with NSAIDs in patients with AS [66]. The continuous treatment group exhibited greater spinal radiographic progression (assessed by mSASSS) compared to the on-demand group (MD 0.49; moderate certainty, Table S5). However, this difference was not statistically significant. In patients with complete sets of radiographs, this difference was even more pronounced (MD 0.8; low certainty, Table S5) [66].

Furthermore, disease activity (assessed with BASDAI) was lower in the continuous versus the on-demand group during 2 years of treatment (MD − 0.5; low certainty, Table S5).

Regarding safety outcomes, total serious adverse events (SAE), SAE related to cardiovascular disorders, and SAE associated with IBD (colitis or Crohn's disease) were not significantly different between both groups (RR 0.91, 95% CI 0.53–1.55; very low certainty; RR 0.33, 95% CI 0.04–3.12; moderate certainty; and RR 0.91, 95% CI 0.53–1.55; moderate certainty; respectively, Table S5).

On the contrary, an RCT by Wanders et al. concluded that continuous NSAIDs use reduced radiographic progression compared to on-demand use in symptomatic patients with AS [67]. However, SAEs were higher among subjects in the continuous-treatment group (19.8%) in comparison with those in the on-demand group (15.5%) [67].

The guideline panel suggests initiating treatment with NSAIDs for at least 4 weeks, followed by on-demand use for patients with persistent symptoms. NSAIDs were assessed as having negligible cost and savings, with a probable reduction in equity, and deemed likely feasible and acceptable. Once NSAIDs are started, periodic monitoring of disease activity and assessing the treatment response are essential. It is also important to consider the potential gastrointestinal, renal, cardiovascular, and other risks associated with NSAIDs use.

Recommendation 5: *For adults with active axSpA requiring non-steroidal anti-inflammatory treatment, we suggest using either standard NSAIDs or COX-2 inhibitors (conditional recommendation, very low certainty evidence).*

Remarks: COX-2 inhibitors may be preferred for patients with a history of gastrointestinal complications or IBD, as they are associated with a lower risk of gastrointestinal side effects compared to regular NSAIDs.

Rationale

This recommendation is informed by a network meta-analysis of RCTs ($N = 3647$) comparing different NSAIDs in the treatment of AS; no significant differences were found in the main findings between diclofenac and two other commonly used NSAIDs, celecoxib and etoricoxib [68].

Regarding the functional ability, diclofenac showed no significant difference compared to celecoxib (MD − 0.47, 95% CI − 3.65 to 2.31; low certainty, Table S6) or etoricoxib (MD

5.29, 95% CI − 2.21 to 12.3; very low certainty, Table S6) [68]. Similarly, pain scores showed non-significant differences: diclofenac had a slightly lower, but non-significant, effect in comparison with celecoxib (MD − 1.66, 95% CI − 6.34 to 3.03; low certainty, Table S6) and a slightly greater, though still non-significant, effect compared to etoricoxib (MD 6.67, 95% CI − 2.2 to 16.13; low certainty, Table S6) [68].

In terms of disease activity, as assessed by the patient's global assessment of disease activity, and treatment response, assessed with ASAS 20, diclofenac again showed no significant difference compared to celecoxib (MD − 1.56, 95% CI − 6.76 to 3.8; low certainty; odds ratio [OR] 1.16, 95% CI 0.77–1.55; respectively, Table S6) or etoricoxib (MD 7.93, 95% CI − 1.74 to 17.43; very low certainty; MD 0.42, 95% CI 0.16–1.08; low certainty; respectively, Table S6) [68].

For total adverse events, the diclofenac group had a higher non-significant incidence compared to celecoxib (OR 1.14, 95% CI 0.65–1.89; low certainty, Table S6) and etoricoxib (OR 1.29, 95% CI 0.48–3.59; low certainty, Table S6). Similarly, gastrointestinal adverse events were observed more repeatedly, but not significantly, in the diclofenac arm in comparison with celecoxib (OR 1.68, 95% CI 0.86–3.13; low certainty, Table S6) and etoricoxib (OR 1.11, 95% CI 0.31–4.06; low certainty, Table S6).

A systematic review assessed the safety of COX-2 inhibitors used for treating rheumatological manifestations of IBD and found no significant difference in the exacerbation of IBD between the COX-2 inhibitors and placebo. After 12 weeks of treatment, the exacerbation rate in the COX-2 inhibitors arm was lower than the placebo (17% vs. 19%, respectively) (RR 0.88, 95% CI 0.45–1.69) [69]. Another study found that 14-day treatment with celecoxib shows no higher relapse rate among patients with ulcerative colitis who had a present or previous history of arthralgia, nonspecific arthritis, or other diseases amenable to NSAIDs treatment [70]. In addition, several studies reported that NSAIDs use was associated with IBD onset or clinical exacerbation [72–73].

The guideline panel suggested using both COX-2 inhibitors (celecoxib, etoricoxib) and NSAIDs for patients with active axSpA. However, they emphasized the importance of regularly monitoring disease activity and adverse events, beside assessing the degree of response. Special consideration should be given to these medications' potential gastrointestinal, renal, and cardiovascular effects.

3. Second-Line Treatments for Adults with axSpA

Recommendation 6: *For adults with active axSpA, we recommend using either TNFi (including infliximab, etanercept, certolizumab, adalimumab, and golimumab), interleukin-17 inhibitors(IL-17is) (ixekizumab, secukinumab, and bimekizumab), or Janus kinase inhibitors (JAKis) (upadacitinib and tofacitinib) (strong recommendation, moderate evidence).*

Rationale

The guideline panel recommended either TNFi therapy, IL-17i, or (JAKi) for adults with active axSpA, acknowledging their efficacy. However, they advised against using JAKi in patients with a history of thrombosis or those at high risk for cardiovascular disease. This recommendation was informed by a large network meta-analysis ($N = 8937$) comparing treatment options for AS [74]. TNFi showed better health status outcomes than JAKi when assessed by ASAS 20 (RR 0.77, 95% CI 0.60–0.99; very low certainty, Table S7), but results were not significant for ASAS 40 or ASAS 5/6 (RR 0.76, 95% CI 0.47–1.19; very low certainty; OR 0.66, 95% CI 0.33–1.26; very low certainty; respectively, Table S7) [74].

An RCT involving 270 patients across 75 centers in 14 countries assessed the efficacy of tofacitinib 5 mg twice daily compared to placebo [75]. Significant improvements were noted in ASAS 20 (RR 1.92, 95% CI 1.42–2.59; moderate certainty, Table S8) and ASAS 40 (RR 3.25, 95% CI 1.99–5.30; moderate certainty, Table S8). Disease activity, assessed by

ASDAS, showed a mean improvement of 0.97 (95% CI −1.164 to −0.776; high certainty, Table S8), while high-sensitivity C-reactive protein (hsCRP) levels decreased by 0.96 (95% CI −1.24 to −0.68; high certainty, Table S8) [75]. Moreover, the tofacitinib group had a greater frequency of partial remission (RR 5.11, 95% CI 1.80–14.56; high certainty, Table S8) and ASAS 5/6 response (RR 5.93, 95% CI 3.17–11.10; high certainty, Table S8). Adverse events were described in 54.9% of the tofacitinib group and 51.5% of the placebo group, with SAE in 1.5% and 0.7%, respectively [75].

On the basis of this evidence, JAKi has demonstrated significant efficacy in decreasing disease activity and symptoms while maintaining favorable safety outcomes, making it a valuable treatment option for axSpA, consistent with other guidelines. However, concerns remain regarding the potential risks of venous thromboembolism and cardiovascular events, particularly in patients with high cardiovascular risk factors or those on long-term JAKi therapy [27, 29].

A cohort study also found similar drug discontinuation rates and 1-year responses between JAKi and TNFi in patients with rheumatoid arthritis (RA) [76]. The guideline panel acknowledged the efficacy of JAKi (e.g., upadacitinib, tofacitinib) for active axSpA but highlighted their high cost. They emphasized the importance of regular monitoring for disease activity (e.g., ASDAS) and adverse events, as well as screening for cardiovascular complications, malignancy, and thrombosis before initiating JAKi. Additionally, other international guidelines recommend avoiding JAKi in patients over 65 or those with high cardiovascular risk [27]. Research priorities include head-to-head trials comparing TNFi and JAKi, as well as long-term remission, safety, and economic evaluations.

The panel also suggested IL-17A inhibitors (e.g., secukinumab, ixekizumab) or IL-17A/F inhibitors (e.g., bimekizumab) for adults with active axSpA.

A network meta-analysis compared bimekizumab's efficacy and safety to other bDMARDs. For ASAS 20 improvement, bimekizumab showed non-significant advantages over ixekizumab (OR 1.01, 95% CI 0.61–1.61; low certainty, Table S9) and secukinumab (OR 1.24, 95% CI 0.86–1.79; low certainty, Table S9). For ASAS 40 improvement, bimekizumab had non-significantly lower odds compared to ixekizumab (OR 0.92, 95% CI 0.57–1.44; low certainty, Table S9) but significantly higher odds compared to secukinumab (OR 1.6, 95% CI 1.01–2.6; low certainty, Table S9). Bimekizumab also showed better partial remission outcomes compared to secukinumab (OR 1.65, 95% CI 1.08–2.51; low certainty, Table S9) [77].

Phase 2 and 3 RCTs have demonstrated that bimekizumab provides rapid and sustained improvement in SpA outcomes without significant adverse events [78, 79].

This evidence highlights the effectiveness of bimekizumab with significant improvements compared to placebo as observed in a ≥ 20% improvement in health status measured by ASAS 20 (OR 3.22, 95% CI 2.3–4.35, moderate certainty, Table S10), 40% improvement measured by ASAS 40 (OR 4.02, 95% CI 3.08–5.19, moderate certainty, Table S10), and partial remission assessed by ASAS-PR (OR 5.02, 95% CI 3.62–6.84, moderate certainty, Table S10) [77].

A recent RCT randomized subjects with active psoriatic arthritis and previous inadequate response or intolerance to TNFi to receive either bimekizumab 160 mg every 4 weeks or placebo. By week 16, 43% of those on bimekizumab reached the American College of Rheumatology 50% Improvement (ACR50), in comparison with 7% in the placebo (adjusted OR 11.1, $P<0.0001$). Among patients with at least 3% body surface area affected by psoriasis, 69% on bimekizumab achieved Psoriasis Area and Severity Index 90 (PASI 90), versus 7% on placebo (adjusted OR 30.2, $P<0.0001$). Treatment-emergent adverse events (TEAEs) were reported in 40% of the bimekizumab group and 33% of the placebo, with no new safety concerns or deaths [80].

While the panel recognized the high cost of IL-17i and their potential to reduce equity, they concluded that bimekizumab is acceptable, feasible, and likely to improve health equity. Larger studies are warranted to provide clearer evidence for effectiveness and safety.

The panel suggested either TNFi therapy, IL-17i, or JAKi for adults with active axSpA, based on their established effectiveness and safety. The

decision should be guided by the safety profile, coexisting comorbidities, extra-musculoskeletal manifestations, patient preference, risk–benefit ratio, and cost considerations.

The strong recommendation for TNFi, JAKi, or IL-17i was supported by high-quality evidence from multiple RCTs demonstrating the efficacy of each drug class compared with the placebo and considering that the overall benefits of them outweigh the potential risks [82–86]. However, the low certainty evidence originated from the cited network meta-analyses, which compared the efficacy of TNFi with JAKi and IL-17i (secukinumab, ixekizumab) with bimekizumab alone, in the absence of direct head-to-head comparisons, to answer the relevant PICO questions.

Recommendation 7: *For adults with active axSpA, we suggest using any TNFis (conditional recommendation, low evidence).*

Rationale

Our recommendation is based on a recent meta-analysis, including 48 articles comparing the different treatment options in patients with AS. The study indicated that TNFi had consistent and significant benefits across multiple clinical outcomes compared to placebo. A significant improvement in disease activity was observed in ASAS 20 (RR 2.2, 95% CI 2.0–2.5; low certainty, Table S11), ASAS 40 (RR 3.1, 95% CI 2.4–4.2; low certainty, Table S11), ASAS 5/6 (RR 5.4, 95% CI 3.9–7.7; low certainty, Table S11), and BASDAI 50 (RR 3.2, 95% CI 2.6–4.0; low certainty, Table S11). In addition, TNFi treatment resulted in an MD of −1.4 (95% CI −1.6 to −1.2; low certainty, Table S11) in BASFI. However, a slight risk of adverse events among patients treated with TNFi was detected (RR 1.2, 95% CI 1.1–1.3; low certainty, Table S11) [74].

However, in previous studies, etanercept did not demonstrate clear efficacy in treating uveitis and has been linked with a high risk of uveitis flares [87]. When comparing the efficacy of anti-TNFα antibodies such as adalimumab and infliximab with a soluble TNF receptor molecule such as etanercept in patients with AS, etanercept treatment triggered new-onset uveitis cases more than adalimumab after a short-term period (26.4% vs. 6.3%; $P=0.024$) [88]. In addition, another study found that patients with AS who received monoclonal TNFi reported infrequent new onset and flare of IBD events, as well as infliximab largely prevented IBD activity. In comparison, those who received etanercept reported a high frequency of new-onset and flares of IBD [89]. Thus, the panel suggests using monoclonal TNFi and avoiding etanercept for cases with concomitant uveitis or IBD.

The guideline panel issued a conditional recommendation, noting that head-to-head trials comparing the efficacy of different TNFi are needed to establish a superior option. Otherwise, the choice of TNFi should rely on the physician's experience and patient preference. In addition, they highlighted that TNFis have a moderate cost. They also indicated that TNFi agents are likely to enhance equity and are probably acceptable and feasible for implementation.

Recommendation 8: *For adults with active axSpA, we suggest using TNFi as monotherapy rather than in combination with NSAIDs (conditional recommendation, low certainty evidence).*

Remarks: Chronic NSAIDs use alongside TNFi does not significantly enhance effectiveness compared to TNFi alone. Additionally, long-term NSAIDs use is associated with serious risks, including gastrointestinal bleeding and renal impairment. The panel advises using NSAIDs on an as-needed basis to control pain unrelated to inflammation, such as pain from degenerative causes.

Rationale

Our recommendation is based on a recent RCT ($N=128$) comparing TNFi alone versus NSAIDs alongside TNFi [90]. Regarding the radiographic progression (assessed by mSASSS), there was no significant difference between the monotherapy versus the combination (MD 0.43, 95% CI −1.49 to 2.34; moderate certainty, Table S12). In addition, the percentage of subjects with new syndesmophytes after 2 years did not differ (RR 0.49, 95% CI 0.2–1.2; low certainty, Table S12) [90].

In addition, there is no significant difference in disease activity changes (BASDAI and ASDAS) between TNFi alone and NSAIDs used with TNFi [90].

The difference in safety outcomes was insignificant between combination therapy and monotherapy. This included SAE (RR 1.2, 95% CI 0.39–3.72; low certainty, Table S12) and study discontinuation due to adverse events (RR 3.86, 95% CI 0.45–33.5; low certainty, Table S12) [90].

Several adverse effects of NSAIDs are reported, such as gastrointestinal, renal, and cardiovascular disorders. Gastrointestinal disorders frequently occur among NSAID users, ranging from minor symptoms such as nausea, dyspepsia, and heartburn to severe gastrointestinal bleeding. Renal side effects of NSAIDs are described with NSAIDs use, including a decrease in glomerular filtration rate, renal papillary necrosis, acute renal failure, acute interstitial nephritis, nephrotic syndrome, chronic renal failure, and fluid retention. In addition, NSAIDs may worsen hypertension and cause myocardial infarction [91].

The guideline panel considered monotherapy to be a probably feasible and acceptable option. Our recommendations align with international guidelines, which advise against using NSAIDs, particularly in patients with well-controlled disease activity [27].

Recommendation 9: *For patients with active nr-axSpA, we recommend using TNFi, (infliximab, etanercept, certozilumab, adalimumab, and golimimab), IL-17i (ixekizumab secukinumab, and bimekizumab), or JAKi (upadacitinib) (strong recommendation, moderate certainty evidence).*

Rationale

This recommendation was informed by a network meta-analysis that depends on RCTs comprising three bDMARDs/tsDMARDs exposure networks (predominantly naïve, naïve, and experienced) to evaluate the effectiveness and safety of the drugs [77].

In a meta-analysis with ten RCTs, significant ≥ 40% and ≥ 20% improvements in disease activity were observed among subjects with nr-axSpA who received TNFi in comparison with those in the placebo group (OR 0.22, 95% CI 0.16–0.29; moderate certainty; OR 0.33, 95% CI 0.26–0.43; moderate certainty; respectively, Table S13). Partial remission rates were greater in patients with nr-axSpA who received TNFi in comparison with the placebo (OR 0.26, 95% CI 0.17–0.37; moderate certainty, Table S13). There was no significant difference between TNFi and the placebo regarding SAE (OR 0.53, 95% CI 0.23–1.12; moderate certainty, Table S13) [77].

Other meta-analyses concluded that TNFi improves disease activity and functional capacity compared to placebo for patients with r-axSpA and patients with nr-axSpA [92].

In the PREVENT study, patients received secukinumab 150 mg (with or without a loading dose) or placebo, followed by open-label secukinumab at week 52. At week 104, minimal and non-significant differences in SI joint inflammation (MD 0.08, 95% CI −0.013 to 0.17; low certainty, Table S14) and spinal inflammation (MD 0.03, 95% CI −0.06 to 0.12; low certainty, Table S14) were observed. However, a sustained reduction in SI joint bone marrow edema was reported at week 16 (MD 0.86), week 52 (MD 1.09), and week 104 (mean [SD] -1.73). Low spinal inflammation was also maintained at week 104 (MD −0.26; low certainty) [93].

On the basis of the PREVENT study, secukinumab achieved a quick and sustained improvement in the signs and symptoms of nr-axSpA without any new or unexpected adverse events [82]. Other IL-17is have demonstrated comparable efficacy and safety. Treatment with ixekizumab was linked with better improvement in the signs and symptoms, sleep, work productivity, and patient-reported outcomes [95–97]. Furthermore, bimkizumab improved clinical response, disease activity, quality of life, and rapid reduction in spinal pain and inflammation, with a large percentage of patients reaching a complete resolution of enthesitis and peripheral arthritis across the axSpA spectrum [84].

To make a decision about JAKi use, the guideline panel relied on a multicenter RCT conducted at 113 sites across 23 countries to study the effectiveness and safety of upadacitinib in nr-axSpA [98]. Upadacitinib demonstrated significantly greater efficacy than placebo at week 14, with a higher ASAS 40 response rate (45% vs. 23%; $P<0.0001$). It also led to significant improvements in tenderness, morning stiffness severity (MD −0.8, 95% CI −1.4 to −0.2; Table S15), and reduced morning stiffness duration (−0.5, 95% CI −1.1 to 0.1; Table S15).

Patients with baseline joint involvement showed improvements in tender and swollen joint counts. Additionally, upadacitinib was associated with a higher rate of partial remission (RR 2.63, 95% CI 1.68–4.14; Table S15) and greater achievement of low disease activity (RR 1.71, 95% CI 1.32–2.24) and inactive disease (RR 3.00, 95% CI 1.83–4.98), all with moderate certainty (Table S15) [98].

Adverse event rates up to week 14 were similar between the upadacitinib and placebo groups (46% vs. 48%; moderate certainty, Table S15), with serious infections or herpes zoster occurring in 1% of patients in both groups. No opportunistic infections, venous thromboembolic events, major cardiovascular events, malignancies, or deaths were reported. While tofacitinib has shown efficacy and safety in r-axSpA, its role in nr-axSpA remains unclear [98].

The guideline panel estimated the potential of TNFi as an effective therapy for patients with nr-axSpA, with a likelihood of being an acceptable and feasible treatment. For the management of active axSpA, the guideline panel recommended using IL-17is at the approved therapeutic doses, including IL-17A inhibitors such as secukinumab 150 mg subcutaneously every 4 weeks or ixekizumab 80 mg every 4 weeks following initial loading doses, as well as the IL-17A/F inhibitor bimekizumab 160 mg every 4 weeks after loading. Dose adjustments may be considered on the basis of clinical response and tolerability. On the basis of moderate certainty evidence, they estimated the potential of upadicitinib as an effective, acceptable, and feasible treatment option for patients with nr-axSpA, which suggested its notable benefit in controlling disease symptoms, with no significant safety concerns reported. Other JAK inhibitors, such as tofacitinib, are approved only for r-axSpA and not for nr-axSpA.

4. Treatment of Adults with Axial Spondyloarthritis (axSpA) and Other Comorbidities

Comorbidities in axSpA are common and have an important effect on patient outcomes, quality of life, and treatment choices [99]. Extra-musculoskeletal manifestations such as IBD and uveitis should be carefully considered in the therapeutic plan [27]. The below recommendations are designed to aid the clinical practice in managing patients with axSpA and these comorbid conditions.

Recommendation 10: *For adults with active axSpA and IBD, we suggest using either monoclonal TNFi or JAKi (upadacitinib or tofacitinib) (conditional recommendation, very low certainty evidence).*

Rationale

As a result of the lack of studies comparing monoclonal TNFi and JAKi in adults with axSpA and IBD, this recommendation was reinforced by the results from two systematic reviews and meta-analyses [89, 100]. The first one (N=1130) assessed the frequency of flares and new cases of IBD in patients with AS who were treated with TNFi compared to placebo [89]. The second meta-analysis (N=3450) compared the efficacy and safety of the different JAKi and placebo in adult patients with IBD [100].

Low rates of new IBD flares were reported during receiving TNFi treatment (0.2 flares/100 patient-years, 95% CI 0.0–0.9; very low certainty, Table S16). TNFis showed a non-significant difference in terms of IBD flares [89].

In patients with Crohn's disease, JAKi significantly improved both induction of clinical remission and clinical response (RR 1.38, 95% CI 1.04–1.83; very low certainty; and RR 1.34, 95% CI 1.13–1.58; very low certainty, respectively, Table S16); however, JAKi did not significantly increase endoscopic remission (RR 2.83, 95% CI 0.76–10.56; very low certainty, Table S16) [100].

For patients with ulcerative colitis disease, JAKi was associated with a statistically significant induction of clinical remission and clinical

response (RR 3.07, 95% CI 2.03–4.63; very low certainty; and RR 1.72, 95% CI 1.38–2.13; very low certainty, respectively, Table S16). They were also associated with a greater likelihood of achieving endoscopic remission (RR 2.43, 95% CI 1.64–3.59; very low certainty, Table S16) [100].

Regarding the safety outcomes, there was no significant difference between JAKi and placebo regarding overall adverse events (RR 1.02, 95% CI 0.97–1.09; low certainty Table S16), SAE (RR 0.82, 95% CI 0.58–1.16; very low certainty, Table S16), and risk of infections (RR 1.4, 95% CI 1.18–1.67; low certainty, Table S16) [100].

Patients with coexisting axSpA and IBD often encounter complex therapeutic challenges, as treatment needs must address both musculoskeletal and gastrointestinal inflammation [101]. Given the chronic nature and impact of IBD on patients' quality of life, the guideline panel considered it essential to evaluate not only musculoskeletal response but also IBD-specific outcomes.

The guideline panel conditionally recommends using either monoclonal TNFi or JAKi for patients with SpA and IBD. They assessed these treatments as offering increased acceptability and feasibility. Further head-to-head comparisons, particularly in patients with SpA and IBD, are needed to strengthen the evidence supporting these treatment options.

Recommendation 11: *For adults with axSpA and active IBD, we recommend against using IL-17i medications over no treatment (strong recommendation, high certainty evidence).*

Rationale

As a result of the lack of direct evidence, this recommendation is according to a pooled analysis of safety data from 21 RCTs ($N=7355$) involving secukinumab (an IL-17i) in three different indications: psoriasis, psoriatic arthritis, and axSpA [102].

Five new cases of Crohn's disease (0.63%) and three new cases of ulcerative colitis (0.38%), with one additional case unspecified, were reported in patients with axSpA exposed to secukinumab. IBD exacerbations were reported in one patient, specifically involving an ulcerative colitis case (moderate certainty, Table S17).

IL-17i is thought to reduce inflammation, but it may also negatively affect the residual function of an already compromised epithelial barrier [104–105]. IBD exacerbations have been reported in patients treated with IL-17i [107–108]. In a small RCT study including 59 patients assigned to either secukinumab or placebo, secukinumab was linked with worsening disease activity and a greater frequency of adverse events in subjects with Crohn's disease [106].

Recommendation 12: *For adults with axSpA and IBD, we suggest using COX-2i over NSAIDs if needed, specifically after the gastroenterology consultation (conditional recommendation, low certainty evidence).*

Remarks: COX-2i are safer than traditional NSAIDs for patients with IBD, particularly regarding gastrointestinal complications.

Rationale

As a result of the lack of direct comparisons between NSAIDs and COX-2i in adults with axSpA and IBD, our recommendation was based on two meta-analyses [109, 110]. The first meta-analysis ($N=1010$) investigated the risk of IBD exacerbation in association with acetaminophen and NSAIDs [109]. It revealed that NSAIDs use was associated with a higher risk of IBD exacerbation compared to placebo (RR 1.29, 95% CI 0.92–1.8; very low certainty, Table S18). The second meta-analysis ($N=368$) focused on the risk of IBD exacerbation in patients using COX-2i [110]. The study found that COX-2i was linked to a lower risk of IBD exacerbation (RR 0.86, 95% CI 0.39–1.88; very low certainty, Table S18).

Our recommendations align with the British Society of Gastroenterology consensus guidelines on the management of IBD, as the evidence suggests that NSAIDs use may be linked with de novo development or exacerbation of pre-existing IBD [111, 112]. Given this risk, caution is advised when prescribing NSAIDs, and COX-2i is recommended as a safer alternative when appropriate for axSpA, especially in subjects with IBD.

Since NSAIDs are a cornerstone of axSpA symptom management, the potential gastrointestinal risks in patients with IBD make this comorbidity particularly impactful on

therapeutic decisions. The guideline panel favored the use of COX-2i over NSAIDs in patients with axSpA and IBD. They also deemed COX-2i as a probable, feasible, and acceptable option for managing these patients, given the potential risks associated with NSAIDs use. Further direct trials comparing NSAIDs and COX-2i, especially in subjects with axSpA and IBD, are needed to support the evidence and provide clearer guidance.

Recommendation 13: *For adults with axSpA and acute episodes of uveitis, we recommend using TNFi monoclonal antibodies (preferably adalimumab or infliximab) over etanercept (strong recommendation, moderate certainty evidence).*

Rationale

The recommendation was developed on the basis of a retrospective study of uveitis in patients with AS [113]. The findings revealed that the treatment with adalimumab and infliximab resulted in a significantly higher relapse-free survival rate of uveitis flares than treatment with etanercept (adalimumab vs. etanercept, $P<0.001$; infliximab vs. etanercept, $P=0.048$, very low certainty, Table S19). A higher prevalence of uveitis onset occurred within 1 year of treatment initiation was reported among patients treated with etanercept (80%) than those treated with adalimumab or infliximab (20%) (RR 2.67, 95%CI 0.69–11.49, very low certainty, Table S19) [113].

In addition, other studies found that using anti-TNF monoclonal antibodies is associated with better outcomes in terms of the incidence or flare rates of uveitis among patients with SpA [115–117].

Another meta-analysis of six studies comparing adalimumab with placebo among patients with non-infectious uveitis. The study indicated that adalimumab significantly lowered the risk of treatment failure (hazard ratio [HR] 0.51, 95% CI 0.41–0.63; moderate certainty, Table S19), visual loss (MD −0.05, 95% CI −0.07 to −0.02; moderate certainty, Table S19), and moderately reduced anterior chamber cell grades (MD −0.29, 95% CI −0.62 to −0.05; moderate certainty, Table S19) and vitreous haze grades (MD −0.21, 95% CI −0.32 to −0.11; moderate certainty, Table S19) [118].

In another meta-analysis, infliximab had a promising result in controlling inflammatory activity and gaining visual acuity in treating refractory non-infectious uveitis [119].

The guideline panel strongly recommends using TNFi monoclonal antibodies (preferably adalimumab or infliximab) over etanercept for treating patients with axSpA and uveitis, which is likely to be an acceptable and feasible treatment option. This recommendation aligns with previous international guidelines [27, 29].

Recommendation 14: *For adults with axSpA and uveitis, we suggest against using JAKi (conditional recommendation, moderate certainty evidence).*

Rationale

Limited data exist regarding the efficacy of JAKi in patients with axSpA and active uveitis.

The recommendation was based on network meta-analysis RCTs of TNFi, IL-17i, and JAKi in axSpA [120].

Evidence of preventing the onset or recurrence of uveitis depended on the incidence rate ratio of anterior uveitis. The analysis based on six RCTs showed a slightly non-significant difference in the incidence of uveitis between JAKi and the placebo (incidence rate ratio [IRR] 0.32, 95% CI 0.06–1.67; moderate certainty, Table S20) [120].

In a cohort study, patients with axSpA treated with JAKi experienced an uveitis exposure-adjusted incidence rate (EAIR) of 6.97 episodes per 100 patient-years, which decreased to 2.35 after treatment [121].

The guideline panel concluded that while treatment may reduce the risk of anterior uveitis, the evidence remains inconclusive because of insufficient clinical data. Therefore, the panel conditionally recommends against the use of JAKi for patients with axSpA and uveitis. Further, well-designed studies are needed to provide more conclusive evidence on the impact of JAKi.

Research and evidence gaps: Despite the clinical importance of comorbidities in axSpA, there is a significant lack of head-to-head trials

assessing treatment outcomes specifically in patients with coexisting IBD or uveitis. More real-world data and prospective cohort studies are urgently needed to guide evidence-based decisions for these subgroups.

5. Management of Adults with axSpA and Specific Manifestations

Recommendation 15: *For adults with axSpA and enthesitis, we suggest using either IL-17i (such as secukinumab, ixekizumab, or bimekizumab), TNFi (infliximab, etanercept, certozilumab, adalimumab, and golimimab), or JAKi (upadacitinib and tofacitinib) (conditional recommendation, moderate certainty evidence).*

Rationale

Indirect evidence was used to develop this recommendation because of the lack of a direct comparison between IL-17i and TNFi. A recent meta-analysis of 18 RCTs ($N=6981$) has examined the efficacy of biological agents for treating dactylitis and enthesitis [122]

Regarding the resolution of enthesitis at week 24, the resolution of enthesitis with TNFi (infliximab, golimumab, adalimumab) or IL-17i (secukinumab and ixekizumab) was evaluated compared to the placebo, respectively. A significant resolution was achieved in patients who were using TNFi (RR 1.93, 95% CI 1.33–2.79; moderate certainty, Table S21) and IL-17i such as secukinumab, and ixekizumab (RR 1.95, 95% CI 1.60–2.38; moderate certainty, Table S21) [122].

In the ACHILLES study, a higher proportion of patients with axSpA achieved resolution of Achilles tendon enthesitis in the secukinumab group. Additionally, maintained improvements of patients reported global disease activity and quality of life up to 52 weeks were observed with an acceptable safety and tolerability profile [123].

Similarly, etanercept showed a significant improvement in the assessment of refractory heel enthesitis in SpA patients after 12 weeks, with no unexpected adverse events. However, there was no significant difference in MRI findings [124].

Furthermore, no prior studies have directly compared the efficacy or safety of JAKi and TNFi in treating enthesitis in patients with axSpA. Therefore, two separate studies, each examining one intervention alone or comparing it to a placebo, were used in developing the recommendation.

A systematic review and meta-analysis of four RCTs ($N=779$) showed a significant improvement in enthesitis (assessed by MASES) among axSpA treated with JAKi compared to the placebo (MD −0.67, 95% CI −1.06 to −0.28; moderate certainty, Table S22) [125].

Adverse events and SAE were observed among (51.6% vs. 47.8%) and (1.36% vs. 1.17%) patients in the JAKi treatment group and placebo, respectively (RR 1.10, 95% CI 0.95–1.27; moderate certainty and RR 0.91, 95% CI 0.27–3.08; moderate certainty; respectively, Table S22) [125]. These findings underscore the satisfactory efficacy and safety profiles of JAKi for the resolution of enthesitis and for improving the physical function of patients with axSpA.

Another cohort study evaluated enthesitis evolution among patients with axSpA treated with TNFi. A reduction in modified MASES (mMASES) was noted among 72% and 70% of patients with axSpA evaluated at 6 and 12 months, respectively (very low certainty, Table S22). Moreover, about 37.9% and 43% of patients with axSpA experienced a resolution of enthesitis at 6 and 12 months, respectively (very low certainty, Table S22) [126].

The reduction of mMASES from baseline was maintained at 6 and 12 months (MD −1, 95% CI −1.35 to −0.6; very low certainty and MD −1.1, 95% CI −1.4 to −0.8; very low certainty, Table S22). Furthermore, the incidence of enthesitis was significantly decreased in all observed anatomical sites except for the Achilles tendon at 6 months and at all sites at 12 months [126].

A scoping literature review that demonstrated that JAKi are effective therapeutic options for managing enthesitis in SpA (Table S23) [127]. Furthermore, an RCT demonstrated that higher rates of enthesitis resolution were reported in patients receiving upadacitinib compared

to placebo at week 24 (59.8% vs. 38.0%, moderate certainty, Table S23). Upadacitinib prevented enthesitis recurrence at week 56 in more than 80% of the patients [128]

Another RCT found that IL-17i has clinically significant improvements in patient-related outcomes. At week 24, a higher proportion of patients receiving secukinumab showed resolution of enthesitis based on the Leeds Enthesitis Index (33.3% vs. 23.5%, OR 1.65 95% CI 0.85–3.25; moderate certainty, Table S23). The mean change from baseline in heel pain to week 24 was greater in patients receiving secukinumab compared to those on placebo (2.8 [SD 3.0] vs. 1.9 [SD 2.7], moderate certainty, Table S23) [123].

Before JAKi and IL-17i approval for axSpA treatment, options for targeted therapy were limited to TNFi as the sole available treatment [27, 28]. While there are now a variety of treatment options, there is a lack of evidence comparing JAKi and IL-17i directly in patients with concomitant axSpA and enthesitis. Large head-to-head comparisons are needed to address this gap in evidence.

Overall, the guideline panel suggests that treatment with either IL-17i, JAKi, or TNFis a probable, feasible, and acceptable therapeutic option for improving enthesitis among patients with axSpA.

Ungraded statement 16*: For adults with axSpA and enthesitis, the use of locally administered corticosteroids can be considered (good practice statement).*

Rationale

This conditional recommendation is based on expert opinion and published weak evidence due to the lack of direct evidence. Even though there is limited evidence on the efficacy or tolerability of entheseal corticosteroid injection in axSpA, the guideline panel suggests local corticosteroid administration could be beneficial.

Four studies with limited sample sizes evaluated the efficacy of entheseal corticosteroid injection in patients with SpA, including patients with other inflammatory arthritis disorders. The patients reported improved heel pain following the corticosteroid injection [130–132]. However, these studies did not assess the tolerability, and atrophoderma was the only reported safety concern observed in one patient [132].

Additionally, Tsechelidis et al. recommended that the decision to administer an entheseal corticosteroid injection, preferably guided by ultrasound (US), should be personalized, and other conservative measures should be explored initially. However, it should be avoided for high-risk patients such as those with ruptured entheses [133].

The guideline panel deemed the intervention to be probably acceptable and feasible. However, the recommendation is conditional and based on clinical practice, indicating the need for further research to explore the efficacy and tolerability of the intervention. Moreover, our recommendation aligns with other international guidelines [27–29, 134].

Recommendation 17: *For pregnant women with active axSpA, we suggest using NSAIDs with caution if there is persistent pain despite approved therapy like TNFi, which is an alternative, safer treatment (conditional recommendation, moderate certainty evidence).*

Remarks: NSAIDs should be used cautiously during pregnancy, and NSAIDs should be avoided during the third trimester due to potential risks such as premature ductus arteriosus closure and reduced amniotic fluid.

Rationale

Scarce data are available regarding pregnancy outcomes among women with active axSpA. Our recommendation was based on an observational prospective analysis of 381 TNFi-naïve women with early axSpA [135]. In the study, 50 women with axSpA continued using NSAIDs. Among them, ten women experienced unfavorable pregnancy outcomes, including four pre-term deliveries and six miscarriages. Only six patients continued to receive TNFi during pregnancy, and only one of them had a miscarriage (OR 1.25, 95% CI 0.13–11.9; very low certainty, Table S24). Moreover, the study highlighted that NSAIDs use during the last 6 months was a risk factor for unfavorable pregnancy outcomes (OR 2.5, 95% CI 1.1–5.0, $P=0.02$) [135].

It is well known that the treatment with NSAIDs during pregnancy is associated with fetal and neonatal negative outcomes. Early fetal exposure to NSAIDs during the first trimester is associated with congenital malformations, implantation abnormalities, or miscarriage. Furthermore, the use of NSAIDs during the third trimester might result in premature closure of the ductus arteriosus, oligohydramnios, prolonged bleeding time in the mother and fetus, and decreased uterine dynamics [136, 137]. However, the limited use of NSAIDs for a few days during the second trimester does not cause any potential risk [138].

Consequently, the guideline panel advocates for the cautious use of NSAIDs for pregnant women with axSpA, especially during the third trimester, and using TNFi as a safe alternative, if available. They estimated that anti-TNFis (such as certolizumab, etanercept, infliximab, and adalimumab) are generally considered safer options for managing axSpA in pregnant women. Among these, certolizumab is regarded as the safest, given its minimal placental transfer, which reduces fetal exposure. Etanercept is closely followed as a relatively safe choice, although it does cross the placenta to a greater extent than certolizumab, but it is still within acceptable limits for pregnancy use. Infliximab and adalimumab are also used during pregnancy but are associated with greater placental transfer compared to certolizumab, which may raise concerns during the third trimester.

According to the recent EULAR recommendations regarding the use of antirheumatic drugs during pregnancy and breastfeeding, it is important to consider the individual effectiveness of each drug as well as its potential transplacental transfer. All TNFis are deemed safe for use during pregnancy. Other biologic agents, such as IL-17i or JAKi, may also be utilized if necessary to effectively manage the mother's condition, given the limited information available on their safety and efficacy during pregnancy. Drugs with insufficient safety data during pregnancy should be avoided [139].

Recommendation 18: *For pregnant women with axSpA and isolated sacroiliitis, we suggest using US-guided SI joint injections after the failure of TNFi therapy over no treatment (conditional recommendation, very low certainty evidence).*

Rationale

Indirect evidence was used to address this question because of the lack of direct evidence of clinical studies examining the efficacy or safety of SI joint injections among pregnant women with axSpA and isolated sacroiliitis. Therefore, our recommendation is based on a recent systematic review of five studies, including 34 pregnant or postpartum women with acute inflammatory sacroiliitis who were non-responsive to conventional therapy [140].

Mostly, all patients were treated by US-guided corticosteroid SI joint injections, except for one patient who underwent manual mobilization of the SI joint. The injected corticosteroid was either betamethasone, methylprednisolone, or triamcinolone acetonide. There was a significant reduction in pain scores following 2–4 injections and increased patient satisfaction (Table S24) [140].

In the general population with axSpA and acute bilateral sacroiliitis, fluoroscopy-guided SI joint steroid injection resulted in a $\geq 50\%$ reduction in pain (assessed by the numeric rating scale score) among 90.9% of the injected patients by the first week. This rate decreased to 65% in 6 months, highlighting the short-term utility of the intervention. However, the rate of pain relief was sustainably higher throughout the study [141].

There was also a non-statistically significant reduction in the use of NSAIDs among the study cohort, suggesting the short-term fluoroscopy-guided SI joint steroid injection could be recommended for patients with axSpA, active sacroiliitis, and severe axial pain. The authors recommended the consideration of recurrent fluoroscopy-guided SI joint steroid injection for pregnant women [141].

Therefore, the guideline panel suggests the consideration of SI joint injection for pregnant women with axSpA and isolated sacroiliitis who failed conventional therapy.

Ungraded statement 19: *For adults with axSpA and active peripheral joint involvement, we advise the use of intra-articular injections of glucocorticoids*

after the failure of conventional therapy (sulfasalazine) over no treatment, while we advise against using systemic glucocorticoids (good practice statement).

Rationale

This recommendation was driven by expert opinion because of the lack of studies among adults with axSpA and active peripheral joint involvement. In addition, the guideline panel advised considering sulfasalazine among patients with axSpA and active peripheral joint as another treatment option. In a previous study, sulfasalazine significantly improved peripheral arthritis in patients with seronegative spondyloarthropathies in terms of the overall response, joint pain, and swelling (RR 1.38, 95% CI 1.14–1.66, RR 1.23, 95% CI 1.02–1.48, and RR 1.98, 95% CI 1.01–1.4). The study also concluded that sulfasalazine is a safe and well-tolerated therapeutic option [142]. The EULAR and Pan American guidelines recommend against using sulfasalazine for patients with purely axial disease. However, they emphasized that sulfasalazine could be considered for patients with active peripheral arthritis [27, 29].

On the other hand, in case of failure of conventional therapy such as sulfasalazine, the guideline panel indicated that intra-articular injections of glucocorticoids could be considered for patients with axSpA and active peripheral joint involvement. A systematic review concluded that intra-articular glucocorticoids were well tolerated and effective in relieving pain and enhancing function among patients with rheumatic and musculoskeletal disorders [143].

Likewise, there is a lack of evidence evaluating the efficacy of systemic glucocorticoids in patients with axSpA and active peripheral joint involvement for a long period. Nevertheless, previous studies concluded that high-dose systemic glucocorticoids were effective in treating SpA. However, a daily regimen of these glucocorticoids was associated with an increased risk of major adverse cardiovascular events in patients with RA [144, 145].

The guideline panel suggested that intra-articular interventions may relieve pain for patients with axSpA, which is likely acceptable for those with axSpA and active peripheral joint involvement. However, the low certainty of evidence underscores the necessity for additional studies that evaluate its efficacy and safety in patients with axSpA. According to the Pan American panel, this procedure should be conducted in specialized centers staffed by experienced professionals. Furthermore, the guideline panel recommends avoiding injections near the Achilles, patellar, and quadriceps tendons [29]. This option is safe and effective for similar inflammatory diseases, such as AS [146].

Conversely, the guideline panel underscored that systemic glucocorticoids should not be considered for patients with axSpA due to their known adverse events. EULAR highlights the modest benefits of short-term high-dose glucocorticoids, tapering over 24 weeks, but advises against prolonged use due to a lack of evidence and potential adverse effects. Similarly, the Pan American panel acknowledges limited evidence supporting long-term glucocorticoid use, stating that the risks outweigh the benefits and discourage the prolonged use [27, 29].

6. Long-Term Management of Adults with Active Spondyloarthritis (axSpA)

Recommendation 20: *For adults with active axSpA who have experienced primary failure on a TNFi, we suggest switching to a non-TNF inhibitor (IL-17i or JAKi) rather than cycling to another TNFi and switching to another bDMARD or tsDMARD, with either the same or a different mechanism of action among patients experiencing secondary failure (conditional recommendation, very low evidence).*

Rationale

In the absence of direct studies comparing the efficacy of switching to a non-TNFi with switching to another TNFi following a primary failure on a TNFi among patients with axSpA, we depended on a prospective multicenter cohort study, which reported a better response to the second TNFi among patients with axSpA with secondary failure to the first TNFi compared to those with primary failure [147].

The study demonstrated a higher risk of achieving inactive disease among those following TNFi discontinuation due to secondary failure compared to those with primary failure (OR 7.3, 95% CI 1.9–27.7; very low certainty, Table S25). In addition, those who discontinued the first TNFi because of adverse events had a nearly nine-fold increased likelihood of achieving inactive disease with the second TNFi (OR 9.1, 95%CI 2.5–33.3; very low certainty, Table S25) [147].

Switching to a different TNFi tends to be less effective for patients who did not respond initially compared to those who responded but later experienced a relapse after using the first TNFi [148].

Studies have shown that both IL-17i and JAKi have been effective for patients with axSpA who fail TNFi treatment [149]. These medications target different pathways involved in the inflammatory process, which can offer an alternative treatment strategy when TNFi is ineffective. For instance, clinical trials have demonstrated that JAKi, such as tofacitinib and upadacitinib, improve disease outcomes in patients with axSpA, including those who have previously failed TNFi [150]. However, the evidence for switching therapies remains limited and of very low certainty. The benefits of non-TNF biologics, such as IL-17i, are also evident, but direct head-to-head comparisons between TNFi and non-TNFi following primary failure are scarce [147].

Thus, while there is support for switching to non-TNF therapies in these patients, further research is needed to fully understand the long-term effects and optimal treatment strategies for those who fail TNFi. Clinical decisions should also consider individual patient factors.

The guideline panel recommended switching to another bDMARD or tsDMARD, with either the same or a different mechanism of action among patients experiencing secondary failure.

They also estimated that switching to treatment with another mode of action, like IL-17i or JAKi, would be better. This approach was also considered probably feasible and aligns with other international guidelines [151].

Recommendation 21: *For adults with axSpA in remission, we suggest tapering treatment after 12 months of sustained remission over no tapering (conditional recommendation, low certainty evidence).*

Rationale

This recommendation was based on the BIODOPT trial, an 18-month, randomized, open-label trial with adult patients with RA, psoriatic arthritis, or axSpA stable on biologics and in low disease activity for ≥ 12 months [152]. Patients were randomized to either disease activity-guided biologic tapering or continuation of baseline biologic groups. About 32% of patients in the tapering group achieved successful tapering at 18 months by managing to taper their biologic dose by ≥ 50% and maintaining low disease activity, compared to only 2% of patients who continued the biologics without tapering [152] (Table S26).

Reducing the biologic dose by half or spacing intervals effectively maintained remission without an increase in flare rates, compared to continuing the biologic agents [154–155].

A recent systematic review included RCTs and real-world evidence, highlighting the beneficial outcomes of tapering of bDMARDs in patients with axSpA who achieve sustained long-term disease remission. A tapering decision and strategy should be shared between the patient and the treating rheumatologist [156].

The guideline panel issued that tapering treatment could be a reasonable approach, especially for those in deep remission, with minimal residual inflammation and a lower risk of disease progression. Close monitoring is essential during tapering to detect early signs of disease flare so treatment can be adjusted accordingly. For patients with a more severe or aggressive disease course or those at higher risk of flares, continuing full treatment may be more appropriate to maintain control and prevent relapses. Ultimately, the decision should be individualized on the basis of disease activity, patient preference, and long-term management goals.

This recommendation is consistent with international guidelines such as EULAR and Pan-American guidelines [27, 29].

Recommendation 22: *For adults with axSpA who have maintained persistent remission for more*

than 12 months, we suggest either tapering or spaced-interval TNFi (conditional recommendation, very low certainty of evidence).

Rationale

To develop this recommendation, we followed an RCT ($N=78$) comparing a weekly low dose of TNFi (etanercept) with a spaced dosing interval of every 2 weeks in patients with SpA who had achieved remission [155].

Results showed no significant difference between the weekly dose and spaced interval groups in terms of disease relapse rates (RR 0.70, 95% CI 0.13–3.77; very low certainty, Table S27) and time to relapse (MD 2.0, 95% CI 0.51–3.49; very low certainty, respectively, Table S27). Similarly, after nearly 2 years of follow-up, no significant difference in disease activity was observed. BASDAI scores indicated comparable outcomes between the groups (MD − 0.20, 95% CI − 0.68 to 0.28, very low certainty, Table S27). Likewise, there was no significant difference in the functional capacity (assessed by BASFI) between the two groups (MD − 0.1, 95% CI − 0.72 to 0.52, very low certainty, Table S27). Additionally, disease remission rates showed no significant difference between the weekly and spaced dosing groups (RR 1.05, 95% CI 0.84–1.3, very low certainty, Table S27) [155].

Functional measures such as the modified Schober test and fingertip-to-floor distance were non-significantly lower in the weekly dose group (MD − 0.20, 95% CI − 1.30 to 0.90; very low certainty; and MD − 0.10, 95% CI − 1.60 to 1.43; very low certainty, respectively, Table S27) [155].

Regarding adverse events, the weekly dose group showed a slightly lower incidence than the spaced interval group (RR 0.97, 95% CI 0.58– 1.61; very low certainty, Table S27) [155].

Both dose reduction and spaced interval dosing help reduce economic burden, minimize side effects, and align with patient preferences. Numerous previous studies have highlighted that halving the etanercept dose after achieving remission is an effective therapeutic approach with considerable economic advantages [158–159].

The guideline panel deemed low-dose TNFi to be likely favorable, estimating them to be a high-cost option but probably feasible.

Recommendation 23: *For adults with axSpA who have maintained persistent remission for more than 12 months, we suggest tapering TNFi therapy rather than discontinuing it (conditional recommendation, low certainty evidence).*

Remarks: Tapering treatment helps reduce healthcare costs, minimize side effects, and address patient preferences.

Rationale

Our recommendation is based on a retrospective cohort study ($N=258$) that aimed to compare outcomes between tapering the dose and discontinuing treatment after achieving clinical remission in patients with SpA on standard-dose etanercept therapy [160]. The maintenance of low disease activity or remission was significantly higher in both the 25% and 50% tapering groups versus the discontinuation group (RR 2.94, 95% CI 1.97–4.38; very low certainty; and RR 1.94, 95% CI 1.26–3.00; very low certainty, respectively, Table S28). Regarding the active inflammatory lesions of the SI joints on MRI, both tapering groups (25% and 50%) showed significantly lower values compared to the discontinuation group (RR 0.14, 95% CI 0.08–0.25; very low certainty, and RR 0.52, 95% CI 0.39–0.69; very low certainty, respectively, Table S28).

The disease activity (as assessed by BASDAI) was significantly lower in both the 25% and 50% tapering groups versus the discontinuation group (MD − 3.00, 95% CI − 3.48 to − 2.51; very low certainty, and RR − 1.00, 95% CI − 1.66 to − 0.33; very low certainty, respectively, Table S28). Similarly, when assessed using Ankylosing Spondylitis Disease Activity Score based on C-reactive protein (ASDAS-CRP), the disease activity was significantly lower in the tapering groups (25% and 50%) compared to the discontinuation group (MD − 1.1, 95% CI − 1.32 to − 0.87; very low certainty; and MD − 0.6, 95% CI − 0.9 to − 0.3; very low certainty, respectively, Table S28).

Additional evidence supports our recommendation, showing that abrupt withdrawal of TNFi

is associated with a higher risk of flares, whereas tapering has been successful in maintaining treatment response [155, 161, 162].

Tapering treatment helps reduce healthcare costs, minimize side effects, and align with patient preferences. Consequently, the guideline panel favored low-dose TNFi, noting probable equity, acceptability, and feasibility benefits, though acknowledging the substantial associated costs. Our guidelines align with existing recommendations from other guidelines [27, 29, 151].

Recommendation 24: *For adults with axSpA in remission for more than 12 months, we suggest tapering JAKi rather than stopping them abruptly (conditional recommendation, low certainty evidence).*

Rationale

There is a lack of evidence comparing the efficacy of JAKi tapering versus stopping JAKi in axSpA; we relied on a meta-analysis identifying controlled trials comparing the safety of the tapering of targeted therapies (bDMARDs or JAKi) with the continuation of the initial treatment regimen in patients with RA or SpA in remission or low disease activity [163]. Five randomized trials assessed the risk of serious infections, indicating no significant increase in serious infections among the tapering group compared to the discontinued group (RR 1.20, 95% CI 0.71–2.00, low certainty, Table S29). Similarly, four randomized trials found no significant difference in severe adverse events among the tapering JAKi group compared to the discontinued group (RR 1.4, 95% CI 0.9–2.2, low certainty, Table S29) [163].

Other studies indicated that discontinuing biological agents led to a higher rate of disease flares in patients with axSpA and long-term remission [154–155].

The guideline panel concluded that tapering JAKi in adults with axSpA is likely to be acceptable and feasible, increasing equity and favoring the intervention. In conclusion, tapering JAKi in adults with axSpA who have been in remission for over 12 months is preferable to abrupt discontinuation, which aligns with international practices, including the considerations outlined in EULAR guidelines [27]. However, the decision should be individualized, taking into account disease activity, the duration of remission, and long-term safety concerns. Further research is needed to strengthen the evidence supporting this approach.

Recommendation 25: *For adults with axSpA in sustained remission or low disease activity for at least 12 months, we suggest using either low-dose IL-17i or spaced intervals of IL-17i (conditional recommendation, low certainty evidence). However, we suggest using a low dose of IL-17i over abrupt discontinuation of IL-17i (conditional recommendation, moderate certainty evidence).*

Rationale

The recommendation was based on an RCT involving 155 patients who achieved remission at week 24. Data revealed that a low dose of IL-17i (ixekizumab) resulted in a higher number of flare-free patients after 64 weeks (RR 1.52, 95% CI 1.16–2.01; low certainty, Table S30) compared to the spaced interval. Additionally, findings indicated that a low dose of IL-17i led to an increasing number of patients without clinically important worsening (ASDAS worsening ≥0.9 per ASAS definition) compared to the spaced interval after 64 weeks (RR 2.28, 95% CI 1.45–3.58; low certainty, Table S30). Furthermore, the study demonstrated that the number of patients with low disease activity was higher among low doses of IL-17i compared to the spaced interval group (RR 1.84, 95% CI 1.33–2.54; low certainty, Table S30) [164].

For safety outcomes, a low dose of IL-17i led to no difference in adverse events compared to the spaced interval assessed with TEAE and severe TEAE (RR 0.81, 95% CI 0.53–1.22, and RR 0.68, 95% CI 0.17–2.68, respectively; low certainty, Table S31) [164]. In a similar manner, another RCT found that tapering NSAIDs and DMARDs by 50% in patients with axSpA in sustained remission is a feasible and effective treatment strategy [165]. Limited studies evaluate the efficacy of low doses of IL-17i compared to stopping IL-17i in patients with axSpA. An RCT involving 155 patients evaluating the effects of stopping IL-17i compared to continuing a low dose with a follow-up period of 64 weeks was

also used in developing the recommendation [164]. The efficacy measured by the proportion of flare-free patients, there was an increase of 156 more flare-free patients per 1000 in the low-dose group (RR 1.29, 95% CI 0.89–1.86, low certainty, Table S31) [164].

Tthe low-dose group demonstrated superior outcomes compared to those who stopped treatment in terms of no clinically important worsening (RR 1.82, 95% CI 1.11–2.30; low certainty, Table S31) [164].

Patients who continued with a low dose of IL-17i showed better outcomes regarding low disease activity compared to those who stopped treatment; over a follow-up period of 64 weeks, 695 per 1000 patients in the low-dose group achieved low disease activity, compared to 453 per 1000 in the group that stopped treatment (RR 1.53, 95% CI 1.03–2.28; low certainty, Table S31) [164].

Moreover, fewer adverse events in the low-dose group were indicated compared to those who stopped treatment (RR 0.851, 95% CI 0.529–1.368; low certainty, Table S31) [164].

Although no studies have specifically assessed the cost-effectiveness of IL-17is in Saudi Arabia, the guideline panel considers them to be an affordable treatment option. They also concluded that a low dose of IL-17i is likely to be an acceptable and feasible strategy. Additionally, the panel emphasized that tapering treatment can help reduce healthcare costs, minimize side effects, and align with patient preferences. It was further noted that abrupt discontinuation of biological treatment in patients with axSpA carries a high risk of disease flare. The panel also indicated that using a low dose of IL-17i is cost-effective and likely to be both acceptable and equitable. On the basis of these considerations, they recommended either gradually reducing the dose or extending the dosing intervals.

Recommendation 26: *For adults with active sacroiliitis and axSpA, we suggest using SI injection of glucocorticoids over no treatment (conditional recommendation, very low certainty evidence).*

Rationale

The recommendation was based on a retrospective cohort study that evaluated 43 with axSpA. Twenty-two patients received SI joint steroid injections (triamcinolone acetonide), while 21 did not receive injections [166].

The study assessing pain reduction by more than 50% using the VAS showed improvements at 1 week (RR 1.73, 95% CI 1.13–2.66; very low certainty, Table S31), 1 month (RR 1.69, 95% CI 0.97–2.95; very low certainty, Table S32), 3 months (RR 1.43, 95% CI 0.88–2.31; very low certainty, Table S32), and 6 months (RR 1.53, 95% CI 0.84–2.80; very low certainty, Table S32) [166].

Similarly, disease activity measured by the BASDAI showed little to no improvement across the same time points. The RR for disease activity improvement ranged from 0.89 (95% CI 0.62–1.30; very low certainty, Table S32) at 1 month to 0.89 (95% CI 0.58–1.35; very low certainty, Table S32) at 6 months. However, safety outcomes were not measured [166].

Though the evidence is very low, the guideline panel suggested that treatment may provide modest benefits in reducing pain and disease activity in axSpA. The guideline panel suggested that glucocorticoid SI injection interventions may provide pain relief as well as an acceptable and feasible option for patients with axSpA. Our findings support the review that corticosteroid injections are effective for treating refractory axSpA associated with sacroiliitis. Given the complex anatomy of the SI joint, image guidance is recommended for injections, as it leads to better outcomes than using anatomical landmarks [167].

The panel suggested glucocorticoid SI joint injections as a local intervention for patients experiencing persistent sacroiliitis symptoms despite systemic therapy. This recommendation does not rule out the option to escalate to a third pharmacologic agent when clinically appropriate. The panel viewed SI injection as a potentially valuable adjunct or alternative in selected cases, particularly when pain is localized and systemic options are limited or contraindicated.

Ungraded statement 27: *For patients with moderate to severe pain following the failure of previously recommended treatments, we advise against the routine use of opioids (good practice statement).*

Rationale

Opioids constitute a category of pharmacological agents with the capacity to alleviate pain under specific conditions and are primarily prescribed for the treatment of moderate to severe pain. However, they are associated with potentially severe side effects and pose a risk of misuse and addiction in specific individuals [168].

On the basis of the expert opinion of ASAS-EULAR guidelines, opioid-like drugs may be considered for pain relief when other treatments are insufficient, though caution is advised with long-term use because of addiction risks [27]. Given the common occurrence of residual pain in clinical practice, more head-to-head trials are needed to strengthen the evidence.

In patients with persistent or unexplained pain despite standard treatment, clinicians should re-evaluate the diagnosis to rule out alternative causes. Additionally, referral to a multidisciplinary pain specialist should be considered to optimize pain management strategies.

For adults with severe pain secondary to structural damage from axSpA, the guideline panel suggested opioid use, especially when other treatments have failed. However, opioids are not recommended for pain associated with active inflammatory axSpA. The guideline panel determined that the benefits of opioids for pain secondary to structural damage likely outweigh the risks when other treatment options are exhausted, although opioids should not be used routinely because of their addictive potential. They noted that opioid use would likely have no impact on health equity and may be an acceptable and feasible option for managing complex pain in axSpA.

7. Monitoring of Adults with Active Spondyloarthritis (axSpA)

Recommendation 28: *For adults above 50 years with axSpA, we suggest evaluation and regular screening for osteoporosis using bone mineral density and fracture risk over no screening (conditional recommendation, very low certainty evidence).*

Remarks: Assessment and management of osteoporosis is essential, particularly in patients with a long disease duration or high-risk groups such as those on corticosteroids or patients above 50 years who are prone to a higher risk of fracture.

Rationale

Our recommendation is based on a cross-sectional study that compares fracture risk assessment using the trabecular bone score in patients with axSpA to matched healthy volunteers, as there is a lack of direct comparative data [169]. The bone mineral density (BMD) showed statistically significant lower values in the axSpA group compared to the healthy volunteer group at the lumbar spine (MD −0.99, 95% CI −0.14 to −0.57; very low certainty, Table S33) and the femoral neck (MD −0.37, 95% CI −0.07 to −0.001; very low certainty, Table S33). However, no significant difference was observed between the groups when assessing BMD at the total hip (MD −0.029, 95% CI −0.007 to 0.01; very low certainty, Table S33). The odds of low BMD or osteoporosis were higher in the axSpA group compared to healthy volunteers at the lumbar spine (RR 1.57, 95% CI 0.53–4.68; very low certainty, Table S33), femoral neck (MD 1.64, 95% CI 0.4–6.75; very low certainty, Table S33), total hip (MD −0.37, 95% CI −0.07 to −0.001; very low certainty, Table S33), and any site (MD 6.71, 95% CI 0.84–53.82; very low certainty, Table S33). However, the differences between both groups did not reach statistical significance.

A recent systematic review found that the prevalence of osteoporosis and fractures in individuals with axSpA ranges from 11.7% to 34.4% and 11% to 24.6%, respectively. It is important to consider risk factors such as steroid use, low levels of 25-OH vitamin D, and alcohol consumption when assessing osteoporosis in patients with axSpA [170].

Other meta-analyses reported a significant increase in BMD at the lumbar spine and hip after initiating TNFi [171, 172]. Haroon et al. reported an increase in the BMD at the lumbar spine by 5.1% after 1 year of initiating TNFi and by 8.6% after 2 years. Similarly, improvements in total hip BMD were noted, with increases of 5.1% after 1 year and 8.6% after 2 years [171].

The guideline panel conditionally recommends evaluation and regular screening for

osteoporosis using BMD and fracture risk, especially in high-risk groups, e.g., those on steroids or above 50 years old who are prone to inflammation or risk of fracture. Large direct comparisons are needed in this area to establish clear guidelines for osteoporosis screening in patients with SpA.

Recommendation 29: *For monitoring disease progression in adults with axSpA, we suggest regular radiological assessments, such as an SI joint X-ray every 2 years, rather than no monitoring. We do not recommend routine follow-up MRIs of the SI joint or spine unless there is uncertainty regarding the source of persistent symptoms or inflammatory activity. In such cases, MRI may help determine the presence of inflammation and guide therapeutic decisions (conditional recommendation, low certainty of evidence).*

Rationale

In the absence of direct evidence comparing regular radiological monitoring versus no radiological monitoring for measuring disease progression in adults with axSpA, we used indirect evidence to address this question. A phase 3 RCT ($N=315$) reported the imaging outcomes of patients with AS and nr-axSpA treated with certolizumab pegol [173]. Among patients with AS, significant disease progression was observed after 204 weeks (MD 0.98, 95% CI 0.34–1.63; moderate certainty, Table S34), with most progression observed within the first 2 years (MD 0.67, 95% CI 0.21–1.13; moderate certainty, Table S34) compared to years 2–4 (MD 0.31, 95% CI 0.02–0.6; moderate certainty; respectively, Table S34) [173].

Similarly, a 2-year longitudinal observational study demonstrated significant radiological progression in patients with AS, as indicated by an increase of ≥2 in the mSASSS compared to baseline ($P=0.001$) [174].

Another study found that X-rays showed a superior specificity of 67.6%, compared to 86.5% (MR) and 97.3% (CT) [175].

The rates of spinal radiographic progression in patients with axSpA can vary; however, in most cases, several years may pass before new bone formation becomes visible on radiographs. Consequently, a minimum follow-up period of 2 years is necessary to evaluate radiographic progression [173, 177–178].

The guideline panel considered regular radiological monitoring to be likely feasible and acceptable, with a probable increase in equity. The recommendation to perform SI joint X-rays every 2 years is intended to monitor structural changes over time. However, as a result of radiation risks and the challenges of assessing disease progression with MRI, the panel does not recommend routine follow-up MRIs unless there is uncertainty about the source of persistent symptoms or inflammatory activity.

8. Non-pharmacological Management for Adults with Axial Spondyloarthritis (axSpA)

Recommendation 30: *For adults with axSpA, we suggest using an anti-inflammatory diet, such as a Mediterranean diet, over a regular diet (conditional recommendation, very low certainty evidence).*

Rationale

The evidence regarding the impact of diet in modulating disease activity and symptoms in SpA remains scarce, and no RCTs have evaluated the effect of the Mediterranean diet on the axSpA. Therefore, this recommendation was based on a monocentric cohort of patients with axSpA who received nutritional guidance on the Mediterranean diet over 6 months [179].

In a non-randomized study, there was a significant association between a ≥ 20% improvement in disease activity (assessed with ASDAS-CRP) and adherence to the Mediterranean diet (OR 6.75, 95% CI 1.80–25.30; very low certainty, Table S35). The absolute difference was 373 more per 1000 patients (95% CI 143–465 more), achieving this improvement. A ≥ 20% improvement in the ASDAS-CRP at month 6 was significantly more frequent in the group that received the Mediterranean diet (17%) compared to the other group (9.5%) ($P=0.020$) [179].

Another cohort study indicated significant improvement in disease activity ($P=0.047$), physical function ($P=0.012$), swollen joint count ($P=0.001$), CRP level ($P=0.006$), and pain ($P=0.006$) among patients with RA who received a Mediterranean diet. In addition, the patients

in the Mediterranean diet group lost 3.0 kg in weight during the trial ($P<0.001$) [180].

Thus, the guideline panel suggested that using an anti-inflammatory diet, such as a Mediterranean diet, is likely to be an acceptable and feasible complementary therapy in patients with axSpA.

Recommendation 31: *For adults with axSpA, we suggest using alternative treatments such as omega-3 and fish oil over no treatment (conditional recommendation, very low certainty evidence).*

Rationale

The evidence regarding the impact of diet in modulating disease activity and symptoms in SpA remains scarce; therefore, the guideline panel issued this recommendation based on a single-center cohort study aimed at exploring associations between nutrient consumption and SpA activity [181].

In a cohort study, SpA activity was assessed with the ASDAS in patients consuming omega-3, indicating lower omega-3 polyunsaturated fatty acids intake was significantly correlated with increased SpA activity (OR 0.73, 95% CI 0.56–0.95; very low certainty, Table S36). However, lower omega-3 polyunsaturated fatty acids intake was not significantly associated with SpA activity assessed by BASDAI (OR 0.79, 95% CI 0.63–1.01; very low certainty, Table S36) [181]. An RCT with a small number of patients indicated that adequate doses of omega-3 fatty acids could decrease the disease activity of AS [182].

Despite the limited evidence, the guideline panel underscored the potential use of alternative treatments like omega-3 and fish oil for adults with axSpA.

Recommendation 32: *For adults with axSpA, we suggest using regular physical therapy and exercise over not using it (conditional recommendation, low certainty evidence).*

Rationale

Physical exercise is considered a crucial non-pharmacological management option for axSpA. It has been shown that regular exercise has a positive effect on disease activity, physical function, and quality of life among patients with axSpA [183].

This recommendation was based on a meta-analysis of RCTs focused on non-pharmacological interventions like physiotherapy, exercise, or spa therapy [184].

In terms of disease activity, eight randomized trials assessed disease activity using the BASDAI over a median follow-up of 12 weeks, revealing lower scores indicating a reduction in disease activity in the physiotherapy group compared to the usual care group (standardized mean difference [SMD] −0.37, 95% CI −0.64 to −0.11; low certainty, Table S36). In five trials, spinal mobility was evaluated using BASMI and showed no significant improvement in the physiotherapy group compared to the usual care group (SMD −0.12, 95% CI −0.33 to 0.08, low certainty, Table S37). Functional limitation, assessed with the BASFI in eight trials, demonstrated a significant increase in functional capacity in the physiotherapy group compared to the usual care group (SMD −0.36, 95% CI −0.61 to −0.12; low certainty, Table S37). However, pain in two trials over a 16-week follow-up showed no statistical difference in the physiotherapy group compared to the usual care group (SMD −0.31, 95% CI −0.88 to 0.25; low certainty, Table S37). Likewise, there was no significant improvement in quality of life among the physiotherapy group compared to the usual care group (SMD −0.09, 95% CI −0.51 to 0.32; low certainty, Table S37).

The findings of previous clinical trials revealed that the performance of any physical therapy is superior to none in patients with active axSpA [185, 186].

Overall, the guideline panel underscored that using regular physical therapy and exercise is a feasible and acceptable non-pharmacological approach for rehabilitation in patients with axSpA. This recommendation is in agreement with other international guidelines, which strongly emphasize the role of non-pharmacological interventions, particularly exercise and supervised physiotherapy, as essential elements in axSpA care [27, 29].

Recommendation 33: *For adults with axSpA, we suggest using active physical therapy (supervised exercise) over home exercise (conditional recommendation, low certainty evidence).*

Rationale

Active physical therapy (i.e., aerobic, muscle strengthening, active range of motion exercises, or functional exercises such as balance exercises) involves exercise programs supervised by a physiotherapist. This process facilitates the transfer of knowledge through instruction, demonstration, and reflection. Patients learn not only what exercises to do but also how to effectively implement them, while having the opportunity to share their feelings and concerns with their physiotherapist. This interaction fosters a trusting relationship between the physiotherapist and the patients, which can enhance the patients' perception of the effectiveness of the exercise programs [184, 187].

This recommendation was based on a meta-analysis of RCTs that evaluated the effectiveness and safety of non-pharmacological interventions supervised by a physiotherapist in patients with AS compared with usual care or home-based exercise programs [184].

In terms of disease activity, no significant benefit emerged from supervised exercise compared to the home-based exercise group (SMD −0.14, 95% CI −0.42 to 0.15; low certainty, Table S38). Regarding spinal mobility, assessed through BASMI in three trials, a significant benefit was detected after supervised training (SMD −0.2, 95% CI −0.77 to 0.37; very low certainty, Table S38). On comparing supervised training and home-based exercise program groups, there was no significant difference in reducing functional limitation (SMD −0.29, 95% CI −0.70 to 0.12; very low certainty, Table S38). Similarly, there was no significant difference in pain reduction between supervised training and home-based exercise program groups (SMD −0.27, 95% CI −0.61 to 0.07; moderate certainty, Table S38). There was a slight improvement in quality of life in the supervised training group compared to the home-based exercise program group (SMD −0.75, 95% CI −1.31 to −0.20; moderate certainty, Table S38) [184].

Recommendation 34: *For adults with axSpA, we suggest active physical therapy over passive physical therapy (conditional recommendation, low certainty evidence).*

Rationale

There is scarce evidence comparing active physical therapy and passive physical therapy in adults with axSpA, which forced the panel to depend on their clinical experience and the published weak evidence. A meta-analysis concluded that active exercise therapy improved disease activity and symptoms compared to placebo in adults with axSpA. A significant improvement was found in ASDAS (weighted mean difference [WMD] −0.44, 95% CI −0.64 to −0.24; low certainty, Table S38), BASFI (WMD −0.49; 95% CI −0.65 to −0.32; moderate certainty, Table S38), BASMI (WMD −0.49, 95% CI −0.87 to −0.11; low certainty, Table S39), BASDAI (WMD −0.78, 95% CI −1.08 to −0.47; low certainty, Table S39), pain (SMD 0.47, 95% CI −0.74 to −0.21; low certainty, Table S39), and fatigue (SMD 0.49, 95% CI −0.71 to −0.27; moderate certainty, Table S39) [188].

Another meta-analysis compared the effect of exercise programs with no intervention in patients with AS and found that pain showed a clinically meaningful reduction with exercise (MD −2.1, 95% CI −3.6 to −0.6).

When evaluating physical function using the BASFI scale, moderate-quality evidence suggests that exercise programs do not result in significant clinically meaningful improvements (MD −1.3, 95% CI −1.7 to −0.9; 7 studies, 312 participants; absolute reduction 13%, 95% CI 17–9%). Additionally, spinal mobility was improved with exercise (MD −0.7 95%, −1.3 to −0.1) [189]. However, disease activity and fatigue showed no significant reduction with exercise (MD −0.9, 95% CI −1.3 to −0.5 and MD −1.4, 95% CI −2.7 to −0.1, respectively) [189].

Passive physical therapy techniques, such as massage, ultrasound, and heat, may help relieve symptoms of axSpA, including pain and stiffness [190, 191]. However, these approaches should complement regular physical activity because methods like deep tissue massage and spinal manipulation can trigger disease flare-ups in patients with axSpA [28, 191]. In addition, passive physical therapy has been associated with only short-term effects [192]. The guideline panel preferred active physical therapy over

passive physical therapy, aligned with Pan American guidelines [29].

The guideline panel demonstrated that supervised exercise is an acceptable and feasible non-pharmacological approach that aligns with other international guidelines [27, 28, 191].

Ungraded statement 35: *For adults with axSpA, smoking cessation is strongly advised to improve general health and enhance the quality of life (good practice statement).*

Smoking was considered a risk factor for the progression and spinal inflammation among patients with axSpA [194–197].

A recent systematic review of 17 articles, including 4694 participants, found that cigarette smoking and smoking intensity were associated with spinal radiographic progression (assessed by mSASSS) in axSpA, especially among heavy smokers (OR 2.75, 95% CI 1.25–6.05 and OR 3.57, 95% CI 1.33–9.6, $P=0.012$) [198].

Moreover, smoking was associated with worse structural damage and progression of physical disability, and it had a negative impact on overall health and pain assessment, morning stiffness, physical mobility, and quality of life [198]. Therefore, the guideline panel strongly recommends smoking cessation among patients with active axSpA.

Ungraded statement 36: *For patients with axSpA, it is essential to provide comprehensive education about the disease to all individuals (good practice statement).*

Patient education is crucial in the management of patients with axSpA. All patients should receive education and guidance to help them understand their disease, treatment options, self-management, and necessary exercises. This empowers them to make informed decisions about their treatment, actively participate in their management plan, enhance their coping strategies and quality of life, and reduce healthcare resource utilization [199, 200].

Several modalities for patient education should be adapted to the patient's culture and social background. A previous survey has recognized prognosis, treatment, and coaching in self-management through a combination of face-to-face contact and self-education as essential educational topics for patients with axSpA. Additionally, it was emphasized that trusting patient–physician relationships and multidisciplinary and interdisciplinary cooperation between physicians are fundamentals for effective educational programs for patients with axSpA [199]. Patient education may also improve disease outcomes, including BASDAI, BASFI, and ankylosing spondylitis quality of life (ASQoL) [201]. Thus, the guideline panel strongly recommends providing guidance and education to all patients with axSpA. They also support aligning with international guidance (e.g., ASAS/EULAR) on the central role of patient education in axSpA, while tailoring recommendations to the Saudi healthcare context [27].

9. Surgical Treatment for Adults with Axial Spondyloarthritis (axSpA)

Ungraded statement 37: *For adults with axSpA experiencing disability or refractory pain due to hip joint structural damage, we advise considering total hip arthroplasty (THA).*

Remarks: THA has a great impact on a patient's mobility and quality of life, but the yield of the surgical intervention depends objectively on individual clinical, surgical risk profile, type of prosthesis/fixation method, and surgical approach (good practice statement).

Rationale

This recommendation was based on expert opinion because of the lack of RCTs that assess the effectiveness of arthroplasty among patients with axSpA. A retrospective cohort with clinical data of 26 young and middle-aged patients with AS, who were treated with THA and followed up for more than 3 years, found that complications such as lower extremity deep vein thrombosis, pulmonary embolism, and deep infection did not occur. In addition, the average HHS was 87.1 ± 13.1 points, the total passive range of motion was $215.0 \pm 22.0°$, and the passive range of flexion was $90.8 \pm 9.3°$, and all these indexes significantly increased compared with pre-treatment data ($P<0.01$) [202]. Moreover, other observational studies have indicated that THA can reduce pain and enhance joint range of motion and function [204–207].

Table 5 Recommendations for treatment strategy of axial spondyloarthritis (axSpA)

Recommendation	Strength of the recommendation	Level of panel agreement %
Phase 1 (initial treatment)		
1. For definite diagnosis of axSpA, we *recommend* initiating NSAIDs therapy for symptomatic patients, titrating to the maximum tolerated dose as a first-line pharmacologic option	Strong recommendation	100
2. For all patients with a clinical diagnosis of axSpA, we *suggest* initiating non-pharmacologic measures, such as physiotherapy, patient education, regular exercise, and smoking cessation	Conditional recommendation	100
3. If the patient showed sufficient improvement after 2–4 weeks with NSAIDs, we *suggest* continuing NSAIDs as demanded with periodic evaluations to confirm stable disease control	Conditional recommendation	100
4. We *suggest* assessing the disease activity with ASDAS-CRP after 2–4 weeks	Conditional recommendation	100
5. For patients with active disease (ASDAS ≥ 2.1) after 2–4 weeks of maximum NSAIDs, we *recommend* moving to phase 2	Strong recommendation	100
Phase 2		
1. If the disease is active (ASDAS ≥ 2.1), we *recommend* initiating either TNFi, IL-17i, or JAKi therapy	Strong recommendation	100
(a) For patients with associated active uveitis, we *recommend* using TNFi (monoclonal antibodies)	Strong recommendation	100
(b) For patients with associated active IBD, we *recommend* using TNFi (monoclonal antibodies) or JAKi	Strong recommendation	100
2. We *suggest* evaluating the patient clinically and with ASDAS every 3–6 months to assess response and confirm disease control	Conditional recommendation	100
3. After starting bDMARDs or tsDMARDs, if the disease activity improved ASDAS more than/equal 1.1 after 3 months, continue the same treatment		
4. After starting bDMARDs or tsDMARDs, if the disease is still active (ASDAS improvement by less than 1.1 after 3 months), we *recommend* moving to phase 3	Strong recommendation	100
Phase 3		
1. Positive endorsement from a rheumatologist is *recommended* to confirm the presence of inflammation and to exclude secondary causes of back pain in this phase	Strong recommendation	100

Table 5 continued

Recommendation	Strength of the recommendation	Level of panel agreement %
2. For patients with primary failure (no initial response to bDMARD/tsDMARD), we *suggest* switching to another bDMARD/tsDMARD with a different mechanism of action	Conditional recommendation	100
3. For patients experiencing secondary failure (initial response followed by loss of efficacy), we *recommend* switching to another bDMARD or tsDMARD, with either the same or a different mechanism of action	Strong recommendation	100
4. If the patient achieved remission or low disease activity, we *recommend* continuing the current therapy and performing regular ASDAS evaluations every 6 months to maintain disease control	Strong recommendation	100
5. For patients in remission (inactive disease for at least 12 months), we *suggest* considering treatment tapering and ensuring ASDAS is regularly checked every 6 months to confirm stability	Conditional recommendation	100

ASDAS Ankylosing Spondylitis Disease Activity Score, *AxSpA* axial spondyloarthritis, *bDMARD* biologic disease-modifying antirheumatic drug, *CRP* C-reactive protein, *IBD* inflammatory bowel disease, IL-*17i* interleukin-17 inhibitor, *JAKi* Janus kinase inhibitor, *NSAIDs* non-steroidal anti-inflammatory drugs, *TNFi* tumor necrosis factor inhibitor, *tsDMARD* targeted synthetic disease-modifying antirheumatic drug

The guideline panel concluded that the benefits of THA in adults with axSpA who experience disability or refractory pain due to structural damage may outweigh the risks. THA has been shown to significantly improve hip function and quality of life. While complications were minimal, the decision for surgery should consider individual clinical factors and surgical risks. This recommendation aligns with EULAR, which advocates for it regardless of the patient's age. Cementless prostheses are especially preferred for younger patients [27].

Ungraded statement 38: *For adults with axSpA and thoracolumbar kyphotic deformity, the decision to proceed with lumbar osteotomy should be guided by the severity of the deformity, the patient's functional status, and a careful evaluation of surgical risks versus benefits (good practice statement).*

Rationale

A retrospective cohort study of patients with AS with thoracolumbar kyphosis who underwent corrective surgery indicated that dural tears occurred in 8.0% of patients (RR 0.96, 95% CI 0.17–5.30). Transient lower extremity weakness was reported in 4.0% of patients (RR 1.44, 95% CI 0.09–21.90), and abdominal tensive lesions occurred in 8% of patients (RR 0.57, 95% CI 0.12–2.73). The sagittal translation was observed in 12% of patients who underwent osteotomy. The mean loss of correction in the global kyphosis was 2.31° in patients who underwent osteotomy [208].

The guideline panel indicated that lumbar osteotomy should be considered for severe deformities resulting in significant functional impairment, pain, or disability unmanageable by conservative methods. In cases of milder deformities or when the risks of surgery outweigh the potential benefits, conservative management with pain control and physical therapy is preferred (on the basis of expert opinion). This recommendation aligns with EULAR, which highlights specialized surgeons to reduce the risk of complications [27]. However, ACR/Spondylitis Association of America/SpA Research and Treatment Network guidelines conditionally

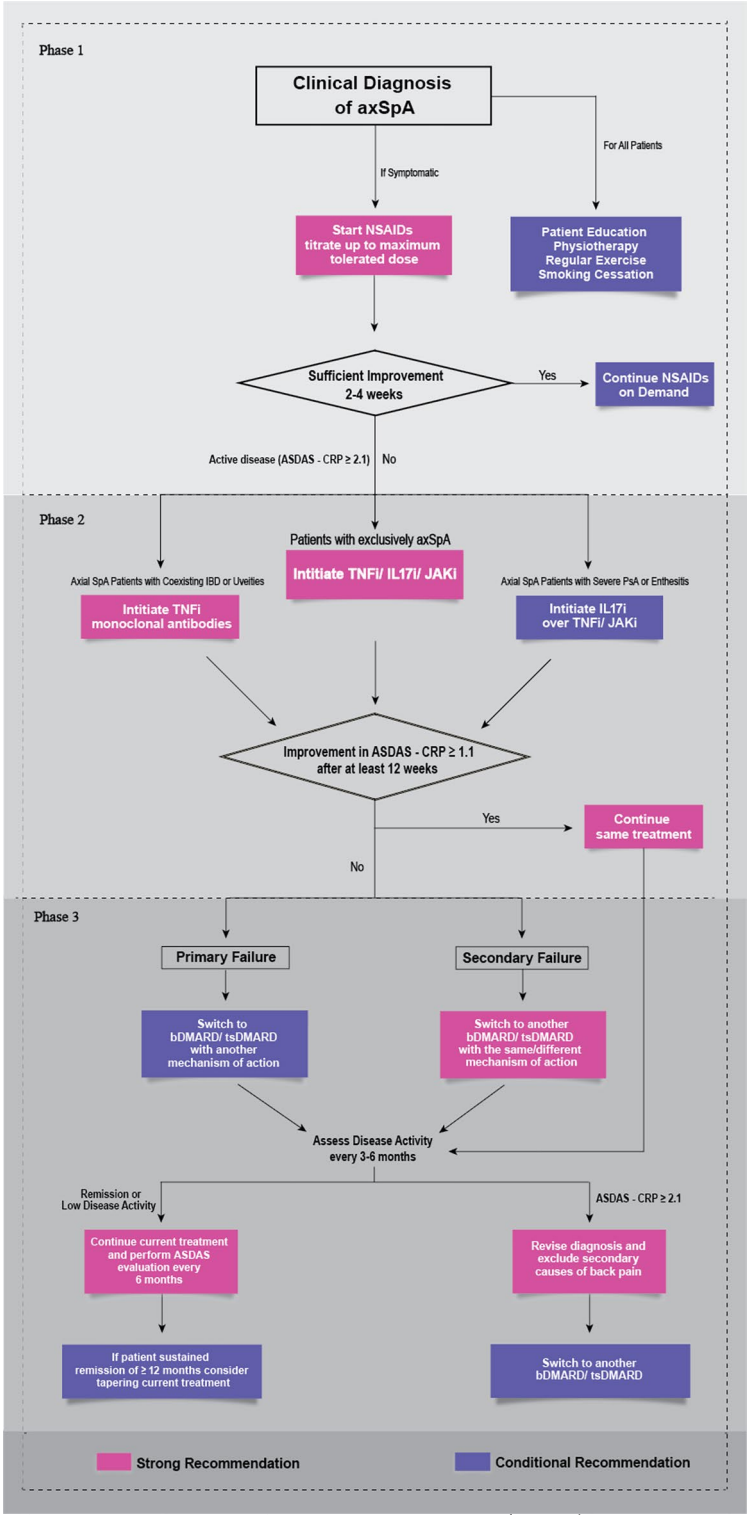

Fig. 1 Recommendations for treatment strategy of axial spondyloarthritis (axSpA). *ASDAS* Ankylosing Spondylitis Disease Activity Score, *ASDAS-CRP* Ankylosing Spondylitis Disease Activity Score based on C-reactive protein, *axSpA* axial spondyloarthritis, *bDMARD* biological disease-modifying antirheumatic drug, *IBD* inflammatory bowel disease, *IL-17i* interleukin-17 inhibitor, *JAKi* Janus kinase inhibitor, *NSAIDs* non-steroidal anti-inflammatory drugs, *TNFi* tumor necrosis factor inhibitor, *tsDMARD* targeted synthetic disease-modifying antirheumatic drug

recommend against elective spinal osteotomy [28].

On the basis of the panel discussion, along with the recommendations and statement developed, a treatment strategy for managing axSpA has been proposed, as outlined in Table 5 and Fig. 1.

DISCUSSION

In these Saudi national guidelines, we present 31 evidence-based recommendations offering a comprehensive framework for the monitoring, management, and treatment of patients with axSpA in Saudi Arabia, as well as seven statements issued based on experts' opinions.

Our guidelines generally align with the recommendations issued by the EULAR and Pan American guidelines. However, we suggest against continuous NSAIDs treatment among patients with active axSpA because continuous treatment may be associated with the risk of gastrointestinal bleeding, kidney injury, and cardiovascular disease, which is in contrast to the EULAR and Pan American recommendations [27, 29].

The guidelines recommend frequent disease monitoring every 3–6 months, particularly when initiating new therapy. ASDAS and treatment-to-target strategies are suggested for measuring disease activity alongside periodic radiological assessments for tracking disease progression. The therapeutic recommendations advocate the use of TNFi, IL-17i, or JAKi in the management of axSpA, with a preference for tapering therapy dosages rather than discontinuing treatment in cases of sustained remission. Special considerations for comorbidities include recommending monoclonal TNFi for patients with concurrent uveitis and advising against IL-17i in patients with coexisting IBD. Furthermore, regular screening for osteoporosis is strongly recommended, especially in high-risk groups.

Regarding patient rehabilitation, the guidelines emphasize the importance of physical therapy, particularly active supervised exercise programs. Anti-inflammatory diets, such as the Mediterranean diet, and the use of omega-3 supplements are also recommended over standard diets for managing disease symptoms; however, these recommendations are based on very low-certainty evidence and should be interpreted with caution. These recommendations aim to enhance patient outcomes by incorporating lifestyle adjustments into comprehensive care.

The development of these guidelines followed an evidence-based approach supported by systematic reviews, meta-analyses where available, and data from RCTs and observational studies. This methodological rigor ensures that the recommendations are applicable in routine clinical settings. A collaborative approach further strengthens this work, involving experts and stakeholders from multiple disciplines to create a well-rounded and practical framework tailored to the Saudi healthcare system.

Despite these strengths, several limitations must be recognized. The guidelines rely on the best available evidence; however, high-quality data are lacking in several areas, particularly in national-level studies and health economic analyses. The reliance on international RCTs and observational studies, as well as the diversity of populations in the source studies and regional variations in healthcare infrastructure, may not accurately reflect local population characteristics and clinical practices, thereby limiting the direct applicability and generalizability of some recommendations to Saudi patients. Thus, future updates of these guidelines should rely on locally generated evidence when applicable. Another key limitation of these guidelines is the absence of patient involvement in the development process. The lack of integration of the patient's perspective when formulating the recommendation may limit its application according to their values and preferences. Therefore, future updates of the guidelines should involve patient representatives and prioritize their input to increase the accessibility and relevance of the guidelines.

Additionally, evidence gaps remain in areas such as the comparative effectiveness of emerging therapies and optimal approaches for managing comorbidities. Implementation may also be challenged by regional disparities in access to

rheumatology services, advanced biologics, and other healthcare resources.

To address these limitations, it is imperative to adopt a dynamic process for updating these guidelines as new evidence and therapeutic options emerge. Leveraging frameworks like GRADE for periodic updates will help integrate future innovations into clinical practice. Future research should focus on filling critical gaps, including the development of localized epidemiological data, direct comparisons of new treatments, and optimal approaches for managing comorbidities. Additionally, Saudi-specific data, including epidemiological studies, health economic evaluations, and real-world treatment outcomes, are highly needed. These efforts will advance best practices in axSpA care and improve patient outcomes across Saudi Arabia.

These guidelines have addressed equity for each PICO question through the GRADE framework. The panel acknowledges that equity may be influenced by various factors, including living in rural or remote areas, social and physical barriers, or having a low socioeconomic status. To address this issue, the guidelines encourage prioritization of individualized treatment decisions, implementing standardized referral pathways, enhancing education of healthcare providers, and integrating social resources to facilitate treatment accessibility [209, 210].

Finally, the successful implementation of these guidelines will require widespread dissemination and training for healthcare professionals. These efforts will include publishing the guidelines in medical journals, presenting them at conferences and scientific meetings, and integrating them into continuing medical education programs. By prioritizing dissemination and professional development, we aim to ensure that these guidelines translate into improved clinical practices and patient care across the nation.

CONCLUSION

These Saudi national guidelines provide an updated set of evidence-based recommendations for the monitoring, management, and treatment of patients with axSpA in Saudi Arabia. They aim to assist policymakers and healthcare professionals in improving the quality of life for individuals living with axSpA. While presenting the best available evidence, these guidelines acknowledge key gaps, including localized epidemiological data and treatment outcomes. This underscores the necessity for future research and regular updates to ensure continued relevance and improved patient care.

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Declarations

Conflict of Interest. Hanan Al Rayes, Nayef Al Ghanim, Hajer Y. Almudaiheem, Mohamed Bedaiwi, Mansour Alazmi, Eman Alqurtas, Haifa F. Alotaibi, Waleed Hafiz, Sultana Abdulaziz, Khalidah A. Alenzi, Bedor A. Al-Omari, Ibrahim Alhomood, Jameel T. Abualenain, and Ahmed H. Al-Jedai declare that they do not have any financial relationships relevant to this article to disclose and that they have no relation or involvement with any organization that holds financial or non-financial interests in the material discussed in this manuscript.

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